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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Viread

### International non-proprietary name: TENOFOVIR DISOPROXIL FUMARATE

### Procedure No. EMEA/H/C/000419/II/0120

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ADV/ADV-R | adefovir dipivoxil (Hepsera, Gilead Sciences)/adefovir dipivoxil resistant |
| AE | adverse event |
| ALT | alanine aminotransferase |
| anti-HBe, | anti-HBs antibody to hepatitis B e or surface antigen |
| AST | aspartate aminotransferase |
| BMD | bone mineral density |
| CFR | Code of Federal Regulations |
| CHB | chronic hepatitis B |
| CHMP | Committee for Medicinal Products for Human Use |
| CLcr | creatinine clearance |
| CMH | Cochran-Mantel-Haenszel |
| CSR | clinical study report |
| DEXA | dual-energy x-ray absorptiometry |
| DNA | deoxyribonucleic acid |
| ETV | entecavir (Baraclude, Bristol-Myers Squibb) |
| EU | European Union |
| FAS | full analysis set |
| FTC | emtricitabine (Emtriva, Gilead Sciences) |
| GCP | Good Clinical Practice |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HIV(-1) | human immunodeficiency virus (type 1) |
| ICH | International Conference on Harmonization of the Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ISCD | International Society for Clinical Densitometry |
| LAM/LAM-R | lamivudine (Epivir, GSK, also 3TC) /lamivudine resistant |
| LLOQ | lower limit of quantitation |
| M=E | missing equals excluded |
| M=F | missing equals failure |
| PCR | polymerase chain reaction |
| PK | pharmacokinetic |
| pol/RT | polymerase/reverse transcriptase |
| SAE | serious adverse event |
| SD | standard deviation |
| SmPC | summary of product characteristics |
| TDF | tenofovir disoproxil fumarate, tenofovir DF (Viread, Gilead Sciences) |
| TFV | tenofovir |
| ULN | upper limit of the normal range |
| US | United States |

# 1. Scientific discussion

## *1.1. Introduction*

Tenofovir disoproxil fumarate (TDF), the oral prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor (NtRTI). After absorption, tenofovir DF is rapidly converted to tenofovir, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate. Tenofovir has an in vitro antiviral activity against retroviruses and hepadnaviruses by inhibiting the reverse transcriptase enzyme hence, by DNA chain termination. Because tenofovir was not well absorbed from the intestine, the prodrug, tenofovir disoproxil, was developed to increase the bioavailability.

Viread was first approved in EU for the treatment of HIV-infected adults in February 2002. Viread was then approved in EU for the treatment of chronic hepatitis B (CHB) in adults in April 2008. Tenofovir is also a component of the fixed-dose combination tablets Truvada (emtricitabine 200 mg/tenofovir DF 300 mg tablet), Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg tablet) and Eviplera (emtricitabine / rilpivirine hydrochloride / tenofovir disoproxil fumarate), which are indicated for treatment of HIV-1 infection. In 2010, the indications for Viread were extended to include patients with hepatitis B with decompensated liver disease. Recently, Viread received authorization for use in HIV-infected children from 2 years of age with NRTI resistance or toxicities precluding the use of first line agents and in HBV-infected adolescents 12 to <18 years of age with compensated liver disease and evidence of active immune disease (Commission Decision 22/11/2012).

The indication for Viread in CHB in adults was based primarily on data from 266 adult subjects with hepatitis B early antigen positive (HBeAg+) compensated CHB and 375 subjects with hepatitis B early antigen negative (HBeAg−) compensated CHB who enrolled in the similarly designed pivotal studies GS-US-174-0102 (HBeAg− subjects) and GS-US-174-0103 (HBeAg+ subjects). In those studies, a limited number of nucleoside-experienced patients (mainly with prior LAM experience) were included. In a pooled analysis of these 2 studies, there were no differences in efficacy response for LAM-experienced (N = 75) compared to LAM-naive subjects (N = 566) after up to 5 years of TDF therapy. Benefit of treatment with TDF has also been observed in 13 patients with LAM-R at baseline in study GS-US-174-0106 that evaluate the efficacy and safety of TDF versus FTC/TDF combination therapy in ADV-refractory patients with or without previous LAM usage.

The purpose of the current submission is to seek a new indication for Viread 245 mg film-coated tablets for the treatment of subjects with lamivudine-resistant (LAM-R) CHB. Accordingly, efficacy, safety, and resistance data in LAM-R subjects with CHB treated with TDF or FTC/TDF are provided.

In addition and in partial fulfilment of follow-up measure (FUM) 234, pharmacokinetic (PK) data are provided for a subset of subjects with mild renal impairment (creatinine clearance [CLcr] 50 to 80 mL/min) treated with TDF.

**Rationale for the study**

The development of nucleos(t)ide analogues has been a major breakthrough for the treatment of CHB, providing effective suppression of viral replication and reducing the risk of long term complications. However, a major limitation of nucleos(t)ide analogues is the selection of HBV resistance variants which can lead to treatment failure and progression to liver disease. The rate of resistance development in treatment-naive patients varies depending on the treatment: up to 80% after 5 years with lamivudine (LAM), up to 29% after 5 years with adefovir dipivoxil (ADV), 40%/20% in hepatitis B e antigen positive/negative (hepatitis B e antigen [HBeAg]+/-) patients after 4 years with telbivudine

(LdT), and 1.2% after 6 years with entecavir (ETV) in naïve patients. To date, resistance to TDF has not been documented.

Thus, the issue of resistance has been considerably weakened with the availability of potent agents with high genetic barrier for resistance, namely entecavir and tenofovir. However, there is an important number of patients who have experienced failure to antiviral therapy, mostly to LAM or ADV that poses problems for antiviral treatment. When resistance develops during treatment of CHB with a nucleos(t)ide analogue, a rescue therapy with the most effective antiviral effect and without cross-resistance is recommended.

In vitro, the ADV-R mutations rtA181V and/or rtN236T confer low level cross resistance to tenofovir (TFV), while the LAM-R mutations rtL180M and/or rtM204V remain sensitive to TFV. Additionally, the ADV/ LAM-R mutation rtA181T remains sensitive to TFV.

There is currently no clear consensus as regards the management of patients with lamivudine resistance and recommendation varies according to therapeutic guidelines.

While the EASL guideline (2009) previously recommended the addition of tenofovir (or adefovir if tenofovir was not available) in patients with lamivudine resistance, the updated guideline (2012) now recommends to switch to tenofovir (or add adefovir if tenofovir is not available) since “most of the experts based on current evidence suggest that switching to tenofovir is as effective as adding tenofovir to lamivudine”. For patients with LAM-R, the current practice guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend the addition of TDF or ADV, while maintaining LAM therapy (or telbivudine) to decrease the risk of subsequent antiviral resistance.

Of note, as regards the management of patients with ADV resistance who had prior LAM experience, EU and US guideline are in line. The EASL guideline recommends a switch to tenofovir and to add a nucleoside analogue. Similarly, in US it is recommended that ADV may be stopped and TDF+LAM, TDF+FTC, or TDF+ETV may be used (durability of response is however unknown).

No large, prospectively-designed clinical study has previously been conducted to establish whether TDF combination therapy (TDF+LAM or TDF+FTC) is the appropriate treatment for LAM-R patients, or conversely, if TDF monotherapy would be equally effective. However, as discussed above, some limited data suggest that TDF monotherapy may be equally effective in the treatment of LAM-R patients.

The MAH is conducting study GS-US-174-0121 to compare the efficacy and safety of TDF monotherapy compared with FTC/TDF combination therapy in the treatment of subjects with CHB who, at the time of screening, were receiving LAM and who had documented LAM-R mutations (rtM204V/I with or without rtL180M). A total of 240 weeks of blinded treatment are planned; the report provided in this submission summarizes the results through Week 96.

## *1.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 1.2.1. Introduction

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity

occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

## 1.2.2. Pharmacology

No additional pharmacology data has been submitted.

## 1.2.3. Pharmacokinetics

No additional pharmacokinetics data has been submitted.

## 1.2.4. Toxicology

No additional toxicology data has been submitted.

## 1.2.5. Ecotoxicity / environmental risk assessment

No update of the ERA has been provided in the current submission. The MAH submitted the ERA previously provided in the setting of the extension of indication to HIV and HBV-infected paediatric patients (dated October 2011). Main data are summarized below:

**Table 1.**

| **Substance (INN / Invented Name): tenofovir disoproxil fumarate** | | | | |
|---|---|---|---|---|
| **CAS-number (if available):** | | | | |
| **PBT screening** | | **Result** | | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | 0.992 at pH 4<br>1.18 at pH 7<br>could not be determined at pH 10 due to the instability of TDF in the buffer phase | | Potential PBT: no |
| ***Phase I*** | | | | |
| ***Calculation*** | **Value** | **Unit** | | **Conclusion** |
| $PEC_{surfacewater}$, default or refined (e.g. prevalence, literature) | 1.5 | µg/L | | > 0.01 threshold |
| ***Phase II Physical-chemical properties and fate*** | | | | |
| **Study type** | **Test protocol** | **Results** | | |
| Adsorption-Desorption | OECD 121 | $K_{oc}$ = 18 L/kg | | |
| Ready Biodegradability Test | OECD 301 | Not readily biodegradable | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | TDF rapidly underwent primary degradation converting to several degradation products | | |
| ***Phase IIa Effect studies*** | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** |
| Algae, Growth Inhibition<br>*Pseudokirchneriella subcapitata* | OECD 201 | NOEC<br>$EC_{50}$ | 14<br>47 | mg/L<br>mg/L |
| *Daphnia, acute immobilisation test / Daphna magnia* | OECD 202 | NOEC<br>$EC_{50}$ | 98<br>≥ 98 | mg/L<br>mg/L |
| Fish Acute Toxicity Test<br>Rainbow trout, *Oncorhynchus mykiss* | OECD 203 | NOEC<br>$LC_{50}$ | 92<br>>92 | mg/L<br>mg/L |
| Daphnia sp. Reproduction Test<br>*Water fleas* | OECD 211 | NOEC<br>$EC_{50}$ | 13<br>21 | mg/L<br>mg/L |
| Fish, Early Life Stage Toxicity Test/<br>Fathead Minnow, *Pimephales promelas* | OECD 210 | NOEC<br>LOEC | 1.9<br>>1.9 | mg/L<br>mg/L |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC<br>$EC_{50}$ | 600<br>940 | mg/L*<br>mg/L* |
| ***Phase IIb Studies*** | | | | |
| Sediment dwelling organism<br>*Chironomus riparius* | OECD 218 | NOEC | 100 | mg/kg |

## 1.2.6. Discussion on non-clinical aspects

No update of the ERA has been provided in the current submission.

The MAH does not give any justification with regards to the new submission as results of the extension of the indication in patients with LAM-R that may result in an increase in environmental exposure. However, this is unlikely to have significant impact given the PEC remains the same by utilization of the default value of Fpen (1%) and in addition the PEC/PNEC ratio is very low (2.5.10-6 to 7.8 x10-4).

More importantly, the MAH submitted an updated ERA for the active ingredient TDF during the MAA of Strilbild (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir) that lead to identify significant limitations to the Viread ERA. Questions have been raised to this purpose. Hence, those questions also apply to this procedure:

- With respect to the ERA for tenofovir disoproxil fumarate (TDF), it is acknowledged that an attempt has been made to clarify the identification of the unknown transformation products at >10%. The applicant suggests that the transformation product at 12 min is potentially tenofovir monoester [mono(POC)-PMPA]. Pursuant to the bioconversion pathway for TDF this transformation product is formed before TFV (=R-PMPA) was generated. However, according to Table 9 of the study report (OECD 308; total system, Taunton River) the 12 min peak was formed after the TFV disappeared. As the actual findings are not in line with the pathway proposed originally, the potential persistent transformation product or peak at 12 min (HPLC) should be formally identified.
- The MAH has indicated that aquatic toxicity studies conducted with TDF produced higher exposures to tenofovir than that achieved if studies were conducted with tenofovir alone and that further studies with tenofovir are not required. However, it is noted that tenofovir was observed as a transformation product after a significant proportion of the TDF partitioned into the sediment and tenofovir, which is a polar dianion, would be expected to have a longer half-life in water. Hence, it is maintained that the MAH should provide a tailored environmental risk assessment for tenofovir with fate studies including the adsorption/desorption study, transformation studies in aquatic systems (OECD 308) and the Early-Life Stage Toxicity Test (OECD 210). Furthermore, additional studies performed in accordance with OECD 308 would facilitate the identification of unknown transformation products, e.g. the 12 min peak and would help to identify the study duration that allows derivation of reliable half-lives. The MAH should ensure that all transformation products ≥10% are identified and that the half-lives are calculated.

  In its response to CHMP, the MAH agrees to conduct a tailored environmental risk assessment for tenofovir, including an adsorption/desorption study (OECD 106), transformation studies in aquatic sediment systems (OECD 308) and an early-life stage toxicity test (OECD 210). Additionally, transformation products ≥ 10% will be fully characterized.

## 1.2.7. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

- With respect to the ERA for tenofovir disoproxil fumarate, it is acknowledged that an attempt has been made to clarify the identification of the unknown transformation products at >10%. The applicant suggests that the transformation product at 12 min is potentially tenofovir monoester [mono(POC)-PMPA]. Pursuant to the bioconversion pathway for TDF this transformation product is formed before TFV (=R-PMPA) was generated. However, according to the study report (OECD 308; total system, Taunton River) the 12 min peak was formed after the TFV disappeared. As the actual findings are not in line with the pathway proposed originally, the potential persistent transformation product or peak at 12 min (HPLC) should be formally identified.
- The MAH should provide a tailored environmental risk assessment for tenofovir with fate studies including the adsorption/desorption study, transformation studies in aquatic systems (OECD 308) and the Early-Life Stage Toxicity Test (OECD 210). Furthermore, additional studies performed in

accordance with OECD 308 would facilitate the identification of unknown transformation products, e.g. the 12 min peak and would help to identify the study duration that allows derivation of reliable half-lives. The applicant should ensure that all transformation products ≥10% are identified and that the half-lives are calculated.

The MAH proposes to submit the study reports by the end of Q2 2015.

The CHMP also considers the following additional measure necessary to address the non- clinical issues:

Within the context of a future variation, to include a statement in Section 5.3 of the Summary of Product Characteristics (SmPC) for all pharmaceutical forms and strengths of Viread, as follows:

"The active ingredient tenofovir disoproxil fumarate and its main transformation products are persistent in the environment".

Overall, there are no non-clinical objections to the approval of this application.

## *1.3. Clinical aspects*

### 1.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The clinical documentation submitted by the MAH consists of one ongoing, long-term (240-week), Phase 3b clinical study GS-US-174-0121.

This study consists of TDF monotherapy or FTC/TDF combination therapy for the treatment of CHB in subjects who, at the time of screening, were receiving LAM and who had documented LAM-R mutations (rtM204V/I with or without rtL180M). In addition, PK profiles of TDF in subjects with mild (CLcr 50 to 80 mL/min) renal impairment have been examined in Study GS-US-174-0121.

**Table 2.** GS-US-174-0121: Summary of Clinical Study in Subjects with CHB Who are resistant to LAM

| Study Number [Ref.] | Design | Study Centers | Study Population | Treatment Regimens | Status |
|---|---|---|---|---|---|
| GS-US-174-0121<br>(n = 280)<br>m5.3.5.1, Week 96 CSR[a] | Randomized, double-blind, double-dummy treatment with TDF 300 mg once daily plus FTC/TDF placebo once daily or FTC 200 mg/TDF 300 mg once daily plus TDF placebo once daily<br>Efficacy assessments include HBV DNA, alanine aminotransferase (ALT), and serology.<br>Safety assessments include adverse events, laboratory tests, vital signs, and hip and spine bone mineral density assessments.<br>Viral resistance and pharmacokinetics (in subset with mild renal impairment) are also assessed. | 62 enrolling centers in US, Canada, Europe, Turkey, and New Zealand | Adults with CHB infection (HBsAg+ for at least 6 months), HBeAg+ or HBeAg–, baseline HBV DNA ≥ 3 $\log_{10}$ IU/mL, ALT < 10 × the upper limit of the normal range (ULN), currently on LAM with confirmation of HBV polymerase/reverse transcriptase (pol/RT) mutation(s) known to confer resistance to LAM (rtM204I/V ± rtL180M) | TDF group:<br>96 weeks of TDF 300 mg plus FTC/TDF placebo (n=141)<br>133/141subjects completed through Week 96<br>FTC/TDF group:<br>96 weeks of FTC 200 mg/TDF 300 mg plus TDF placebo (n=139)<br>125/139 subjects completed through Week 96 | 240-week randomized treatment period ongoing; all continuing subjects have completed 96 weeks |

a GS-US-174-0121 Week 96 Clinical Study Report (CSR), dated 12 June 2012.

### 1.3.2. Pharmacokinetics

In efficacy study GS-US-174-0121, a PK sub-study evaluated the pharmacokinetics of TFV in subjects with calculated creatinine clearance (Clcr) 50–80 mL/min (see further).

### 1.3.3. Pharmacodynamics

No new data were provided.

### 1.3.4. PK/PD modelling

No new data were provided.

### 1.4.1. Main study

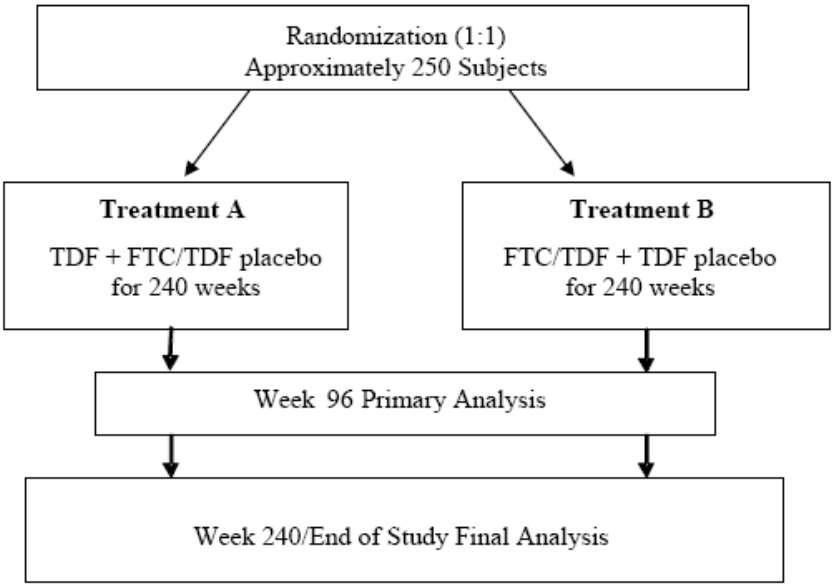
A Phase 3b, Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects with Chronic Hepatitis B who are Resistant to Lamivudine

#### *Methods*

Study GS-US-174-0121 is an ongoing Phase 3b, randomized, double-blind, double-dummy, 240-week study comparing the antiviral efficacy, safety, and tolerability of TDF versus the fixed-dose combination of FTC/TDF for the treatment of CHB infection in LAM-R subjects. Eligible subjects had to be currently receiving LAM and have genotypic evidence of LAM resistance (confirmed LAM-R associated mutation[s] [rtM204V/I ± rtL180M] in the HBV polymerase/reverse transcriptase [pol/RT] gene, and an HBV DNA level of ≥ 3 log10 IU/mL at screening.

Randomization was stratified by hepatitis B early antigen (HBeAg) status (negative or positive) and alanine aminotransferase (ALT) level (≥ 2 × upper limit of normal range [ULN] or < 2 × ULN) at screening.

**Figure 1.**




## *Study participants*

The study enrolled adult subjects (18 to 75 years of age) with CHB infection (HBsAg+ for at least 6 months), HBeAg+ or HBeAg− status, and HBV DNA ≥ 3 log10 IU/mL at screening. Subjects were required to have CLcr ≥ 50 mL/min, ALT < 10 × the upper limit of the normal range (ULN), and no evidence of hepatocellular carcinoma. Subjects must not have had serological evidence of co-infection with hepatitis C virus, HIV, or hepatitis D virus. Subjects with decompensated liver disease, or who were pregnant or breastfeeding, were excluded from the study.

Eligible subjects had to be currently receiving LAM at screening, with confirmation of HBV pol/RT mutation(s) known to confer resistance to LAM (rtM204I/V ± rtL180M) by central laboratory assessment prior to randomization. Prior or current ADV treatment of ≤ 48 weeks (inclusive of ADV+LAM combination therapy) at screening was allowed. Previous treatment with interferon must have ended at least 6 months prior to screening.

The study includes 62 centres in North America (United States and Canada), Europe (Austria, Bulgaria, Czech Republic, Germany, Greece, Hungary, Poland, Romania, Serbia, Spain, and Turkey), and New Zealand.

Study Period: 30 September 2008 (First subject screened) to 02 December 2011 (Last subject observation for Week 96 report).

## *Treatments*

Subjects were randomized in a 1:1 ratio to receive one of the following treatments:

- TDF 300 mg once daily plus FTC/TDF placebo once daily
- FTC 200 mg/TDF 300 mg once daily plus TDF placebo once daily

Study drugs can be taken without regard to food.

## *Objectives*

The primary objective of this study was as follows:

- To compare the antiviral efficacy against hepatitis B virus (HBV) of once-daily tenofovir disoproxil fumarate (TDF) versus once-daily emtricitabine (FTC) plus TDF combination treatment in subjects with lamivudine (LAM) resistance

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of TDF versus FTC plus TDF combination treatment in subjects with LAM resistance
- To evaluate the biochemical and serological responses to TDF versus FTC plus TDF in subjects with LAM resistance
- To compare changes in the resistance profile of each treatment group over the duration of the study
- To evaluate the steady-state pharmacokinetics of tenofovir (TFV) in subjects with LAM resistance

The pharmacokinetic (PK) substudy objective of this study was as follows:

- To evaluate the pharmacokinetics of TFV in subjects with calculated creatinine clearance (CLcr) 50–80 mL/min

## *Outcomes/endpoints*

**Efficacy**

The primary efficacy endpoint for this study was the percentage of subjects with HBV DNA < 400 copies/mL at Week 96 based upon analysis of plasma using the Roche COBAS TaqMan HBV test for use with the High Pure System. The lower limit of quantification for this PCR-based HBV DNA assay is 169 copies/mL (29 IU/mL).

Among secondary efficacy endpoints analyzed at Week 96: HBV DNA < 169 copies/mL (29 IU/mL); HBV DNA level and change from baseline; Normal ALT (≤ ULN) and normalized ALT; Virologic breakthrough; HBeAg loss and seroconversion; HBsAg loss and seroconversion; Genotypic evidence of TDF resistance mutation(s) development

**Pharmacokinetics**

Plasma samples were collected from subjects in the PK substudy at 0 (predose), 1, 2, 4, 6, and 8 hours postdose at a single clinic visit occurring at Week 4 or anytime thereafter. Subjects were instructed to take their daily dose of study drug at the same time as the 0 hour PK sample for at least 2 days prior to the visit.

**Safety**

Adverse events, clinical laboratory tests, and vital signs were evaluated at each study visit. Hip and spine bone mineral density (BMD) was measured via dual-energy x-ray absorptiometry (DEXA scan) at baseline and Weeks 24, 48, 72, and 96 (only required at sites capable of DEXA scans).

## *Sample size*

A 2-sided large-sample normal approximation test of proportions with 125 subjects per treatment group would have had at least 80% power to detect a difference of 20% between the groups, assuming response rates of 50% and 70% in the TDF and FTC/TDF groups, respectively.

The actual number of subjects enrolled into this study was 280, which was 30 subjects over the planned enrolment limit. With this increase in the sample size, the study had at least 90% power to detect a difference of 20% between the groups, assuming response rates of 50% and 70% in the TDF and FTC/TDF groups, respectively.

## *Randomisation*

Two hundred and eighty subjects were randomized in a 1:1 ratio to receive TDF plus FTC/TDF placebo once daily or FTC/TDF plus TDF placebo once daily.

Randomization was stratified by HBeAg status (negative or positive) and alanine aminotransferase (ALT) level (≥ 2 × ULN or < 2 × ULN) at screening.

A centralized randomization procedure was used whereby numbered kits containing bottles of study drug were assigned to subjects via an interactive voice response system according to the randomization code

This was a double-blind, double-dummy study. Subjects were assigned a subject number at the time of randomization. All pre-baseline and baseline tests and procedures were completed prior to the receipt of the first dose of study drug. Initiation of treatment with study medication took place on the day of the baseline visit.

## *Statistical methods*

### Analyses of efficacy

The primary efficacy analysis of the number and percentage of subjects achieving HBV DNA < 400 copies/mL at Week 96 was performed after the last subject reached Week 96. The difference between the TDF and FTC/TDF treatment groups was evaluated using a Cochran-Mantel-Haenszel (CMH) test, controlling for randomization strata, on the FAS with missing = failure (M=F) approach. A supportive analysis of the primary efficacy endpoint was conducted using FAS, excluding missing data (missing = excluded [M=E]).

The endpoint of HBV DNA < 169 copies/mL was analyzed using the same approach as for the primary efficacy endpoint. Both an M=E and an M=F approach was used for analyses of the following secondary categorical endpoints: HBV DNA < 169 copies/mL, ALT normal, and ALT normalized. An M=F approach was used for HBeAg/HBsAg loss and seroconversion endpoints.

The primary analysis set used for the safety analyses (safety analysis set) included all randomized subjects who received at least 1 dose of study drug, and included all data collected during the course of the study (on-treatment and during treatment-free follow-up). The safety analysis set and a modified safety analysis set, including all randomized subjects who received at least 1 dose of study drug and who did not have a DEXA baseline assessment violation, were used for the BMD analyses.

Tests of homogeneity across treatment groups (TDF vs FTC/TDF) were performed for each demographic and baseline characteristic. A chi-square test was used for categorical variables, and a Wilcoxon rank-sum test was used for continuous variables.

### Protocol amendments

The original study protocol was amended 4 times; the first two amendments occurred prior to the start of the study. The HBV DNA entry threshold was reduced from $10^5$ copies/mL to $10^4$ copies/mL to

reflect the current standard of treatment for either switching or adding on to therapy in patients with resistance to current anti-HBV therapy.

During the double-blind treatment phase and two additional changes to the protocol were done:

- A third amendment was done where the entry criteria for the lower threshold of HBV DNA was changed again from ≥ 4 log10 copies/mL to ≥ 3 log10 IU/mL, as current treatment practices were such that this cutoff was used more often in a clinical setting to guide treatment change. In addition, exclusion criteria relating to laboratory values used to define hepatic decompensation were made less stringent to permit enrollment of compensated cirrhotics.
- Analysis of the primary endpoint was modified to occur at Week 96 and was not to be conducted using group sequential testing annually (ie, every 48 weeks) beginning after the last subject reached Week 48. A Week 48 group sequential analysis was not conducted in lieu of the change in endpoint

## *Results*

### Participant flow

Due to a high screen failure rate and the large number of investigational sites participating in the trial, a total of 752 subjects were screened to finally enrol the planned sample size (250 subjects). 280 subjects were finally randomized and treated (141 subjects received TDF once daily [TDF group], and 139 subjects received FTC/TDF once daily [FTC/TDF group]).

A total of 258 subjects (94.3% of subjects [133/141] in the TDF group and 89.9% of subjects [125/139] in the FTC/TDF group) completed the study through Week 96.

Twenty-two subjects discontinued the study prior to completing 96 weeks of study treatment. Of these, 5 subjects discontinued due to safety, tolerability, and efficacy reasons at or before Week 96 (1 subject in the TDF group and 3 subjects in the FTC/TDF group experienced an AE leading to discontinuation. Two of these subjects subsequently died).

**Figure 2.** GS-US-174-0121: Disposition of Study Subjects (all screened subjects).

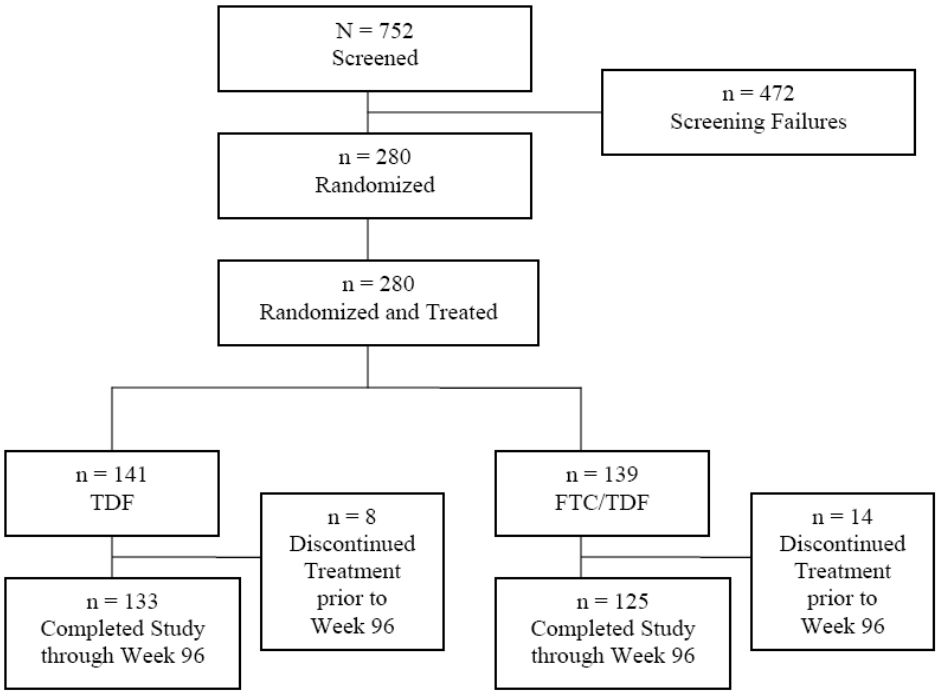



**Table 3.** GS-US-174-0121: Disposition of Subjects (Full Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| Subjects Screened | | | 752 |
| Subjects Randomized | 141 (100.0%) | 139 (100.0%) | 280 (100.0%) |
| Subjects Randomized and Treated | 141 (100.0%) | 139 (100.0%) | 280 (100.0%) |
| Randomization Strata | | | |
| Negative HBeAg status; ALT level < 2 x ULN | 58 ( 41.1%) | 57 ( 41.0%) | 115 ( 41.1%) |
| Positive HBeAg status; ALT level < 2 x ULN | 49 ( 34.8%) | 49 ( 35.3%) | 98 ( 35.0%) |
| Positive HBeAg status; ALT level ≥ 2 x ULN | 18 ( 12.8%) | 17 ( 12.2%) | 35 ( 12.5%) |
| Negative HBeAg status; ALT level ≥ 2 x ULN | 16 ( 11.3%) | 16 ( 11.5%) | 32 ( 11.4%) |
| Subjects in Safety Analysis Set | 141 (100.0%) | 139 (100.0%) | 280 (100.0%) |
| Completed Week 96 Study Treatment Period | | | |
| Yes | 133 ( 94.3%) | 125 ( 89.9%) | 258 ( 92.1%) |
| No | 8 ( 5.7%) | 14 ( 10.1%) | 22 ( 7.9%) |
| Reason for Not Completing Week 96 Study Treatment Period | | | |
| Protocol Deviation | 2 ( 1.4%) | 3 ( 2.2%) | 5 ( 1.8%) |
| Safety, Tolerability, or Efficacy Reasons | 1 ( 0.7%) | 4 ( 2.9%) | 5 ( 1.8%) |
| Withdrew Consent | 2 ( 1.4%) | 3 ( 2.2%) | 5 ( 1.8%) |
| Investigator's Discretion | 2 ( 1.4%) | 2 ( 1.4%) | 4 ( 1.4%) |
| Lost to Follow-up | 0 | 2 ( 1.4%) | 2 ( 0.7%) |
| Study Discontinued by Sponsor | 1 ( 0.7%) | 0 | 1 ( 0.4%) |
| Subject Never Dosed with Study Drug | 0 | 0 | 0 |
| Seroconversion | 0 | 0 | 0 |

Note: Denominator for percentages was the number of randomized and treated subjects.

Programming Details: ...\version5\prog\t-disp.sas v9.2 Output file: t-disp.out 11MAY2012:14:18
Source: Section 15.1, Table 1.2; Appendix 16.2, Listings 1.2 and 1.19

Over 80% of screen failures were due to either lack of documented LAM-R and/or not receiving current treatment with LAM, or were due to having an insufficient HBV DNA level. By establishing these strict criteria for Study 121, it was the purpose to ensure that the population of subjects included in this study was highly reflective of the population of patients with LAM-R in clinical practice.

## Recruitment

### Conduct of the study

A total of 120 of 280 subjects (42.9%) had a least one important protocol deviation during the study (Table 8-3). A higher rate of subjects in the FTC/TDF group (48.9%) than in the TDF group (36.9%) had at least one important protocol deviation.

**Table 4.** GS-US-174-0121: Important protocol deviations (Safety Analysis Set)

| Deviation Type | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| **Number (%) of subjects with at least 1 important protocol deviation in any category** | **52 (36.9%)** | **68 (48.9%)** | **120 (42.9)** |
| Protocol compliance | 28 (19.9%) | 34 (24.5%) | 62 (22.1%) |
| Dual x-ray absorptiometry | 18 (12.8%) | 18 (12.9%) | 36 (12.9%) |
| Study procedures not correctly performed or completed | 8 (5.7%) | 13 (9.3%) | 21 (7.5%) |
| Informed consent | 4 (2.8%) | 5 (3.6%) | 9 (3.2%) |
| Drug management | 3 (2.1%) | 3 (2.2%) | 6 (2.1%) |
| Drug compliance | 3 (2.1%) | 9 (6.5%) | 12 (4.3%) |
| Inclusion criteria | 26 (18.4%) | 30 (21.6%) | 56 (20.0%) |
| Deviations from inclusion criteria about the previous and current HBV treatment | 16 (11.3%) | 19 (13.7%) | 35 (12.5%) |
| Enrollment under forthcoming Amendment 3 | 8 (5.7%) | 9 (6.5%) | 17 (6.1%) |
| Deviation from other inclusion criteria | 3 (2.1%) | 3 (2.2%) | 6 (2.1%) |
| Received prohibited concomitant medications | 2 (1.4%) | 9 (6.5%) | 11 (3.9%) |

NOTE: The total number of subjects with at least one important protocol deviation is presented for each deviation category. Subjects are counted only once per category. Since a subject may occur in more than 1 category, column totals are not generally simple sums of the subcategories.

Source: Appendix 16.2, Important Protocol Deviation List

A total of 56 of 280 subjects (20.0%) were enrolled despite violation of at least one inclusion criterion. Inclusion criteria deviations included the following: 2 subjects were enrolled and randomized to the TDF group in the absence of LAM-R and for this reason these subjects were discontinued from the study. Subject 1069-4082 was then confirmed to have the mutation M204I at baseline. Three subjects (1 randomized to TDF, 2 subjects randomized to FTC/TDF) were enrolled with HBV DNA < 1000 IU/mL at screening. One subject randomized to FTC/TDF was enrolled with a platelet count and an albumin value lower than defined in the inclusion criteria. A total of 17 subjects (8 in the TDF group and 9 in the FTC/TDF group) were enrolled under Protocol Amendment 3 which had not yet been approved by the IRB at the time of their enrolment. This deviation occurred across 11 study sites. Deviations from management of previous and current HBV treatment included the following: 31 subjects (14 in the TDF group and 17 in the FTC/TDF group) did not meet the inclusion criteria regarding previous allowed anti-HBV treatment. Additionally, 4 subjects stopped LAM at an inappropriate time (2 subjects

randomized to TDF and 2 to FTC/TDF discontinued treatment with LAM before baseline; the remaining subject randomized to FTC/TDF continued treatment after baseline for approximately 4 weeks).

**Baseline data**

Demographics and baseline characteristics

Overall, demographics and baseline characteristics were similar between the TDF and FTC/TDF treatment groups. Subjects were predominantly were predominantly male (75.4%), with a mean age of 46.7 years (range of 18 to 73 years), and were white (61.4%) or Asian (33.6%). Overall, mean (standard deviation [SD]) years positive for HBV was 10.8 (7.73) years. The majority of subjects were enrolled at sites in Europe (60.4%).

Prior to randomization, subjects had to be receiving LAM with confirmation of HBV pol/RT mutation(s) known to confer resistance to LAM (rtM204V/I ± rtL180M). At baseline, the median number of days of prior LAM therapy overall was 1229.0 days. Eligible subjects were also allowed to have had prior or current ADV treatment of ≤ 48 weeks at the time of screening (inclusive of combination ADV+LAM). Approximately twice as many subjects had received prior treatment with ADV in the FTC/TDF group compared with the TDF group (28.1% vs 15.6%, respectively [p = 0.012]); the clinical significance of this difference is unknown. Prior interferon therapy was reported for 28.6% of all subjects.

The mean baseline HBV DNA value overall was 6.46 log10 copies/mL. Overall, the majority of subjects (213/280) had ALT levels < 2 × ULN at baseline. Similar proportions of subjects were HBeAg− (52.5%) and HBeAg+ (47.5%). All subjects were HBsAg+ at baseline. The mean (SD) years positive for HBV was 10.8 (7.73) years. The most common baseline HBV genotype in both treatment groups was genotype D (44.7%). Genotype A was present in a lower percentage of subjects in the TDF group compared with the FTC/TDF group (19.0% vs 25.0%, respectively). Genotype B was present in a higher percentage of subjects in the TDF group compared with the FTC/TDF group (19.0% vs 8.1%, respectively). Genotype C was present in 19.0% of subjects overall, and within a similar proportion of subjects within each treatment group (TDF group, 18.2%; FTC/TDF group, 19.9%). One subject in the TDF group had genotype E and 1 subject in the FTC/TDF group had genotype H. For 7 subjects, baseline viral genotype data was missing.

**Table 5.** GS-US-174-0121: Baseline Disease Characteristics (Safety Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) | p-value |
|---|---|---|---|---|
| Baseline HBV DNA (Log10 copies/mL) | | | | |
| N | 141 | 139 | 280 | 0.58 |
| Mean (SD) | 6.40 (1.826) | 6.53 (1.968) | 6.46 (1.896) | |
| Median | 6.27 | 6.81 | 6.39 | |
| Q1, Q3 | 4.70, 8.31 | 4.58, 8.44 | 4.66, 8.38 | |
| Min, Max | 3.37, 9.62 | 2.52, 10.12 | 2.52, 10.12 | |
| Baseline ALT (U/L) | | | | |
| N | 141 | 139 | 280 | 0.47 |
| Mean (SD) | 71.4 (91.02) | 87.1 (147.53) | 79.2 (122.41) | |
| Median | 46.0 | 51.0 | 48.0 | |
| Q1, Q3 | 29.0, 78.0 | 31.0, 83.0 | 30.0, 79.0 | |
| Min, Max | 12.0, 844.0 | 8.0, 1302.0 | 8.0, 1302.0 | |

| | | | | |
|---|---|---|---|---|
| Baseline HBeAg | | | | |
| Negative | 76 ( 53.9%) | 71 ( 51.1%) | 147 ( 52.5%) | 0.64 |
| Positive | 65 ( 46.1%) | 68 ( 48.9%) | 133 ( 47.5%) | |
| Baseline Anti-HBe | | | | |
| Positive | 74 ( 98.7%) | 68 (100.0%) | 142 ( 99.3%) | 0.34 |
| Negative | 1 ( 1.3%) | 0 | 1 ( 0.7%) | |
| - Missing - | 66 | 71 | 137 | |
| Genotype | | | | |
| A | 26 ( 19.0%) | 34 ( 25.0%) | 60 ( 22.0%) | 0.096 |
| B | 26 ( 19.0%) | 11 ( 8.1%) | 37 ( 13.6%) | |
| C | 25 ( 18.2%) | 27 ( 19.9%) | 52 ( 19.0%) | |
| D | 59 ( 43.1%) | 63 ( 46.3%) | 122 ( 44.7%) | |
| E | 1 ( 0.7%) | 0 | 1 ( 0.4%) | |
| H | 0 | 1 ( 0.7%) | 1 ( 0.4%) | |
| - Missing - | 4 | 3 | 7 | |
| Previous Interferon Therapy | | | | |
| No | 102 ( 72.3%) | 98 ( 70.5%) | 200 ( 71.4%) | 0.73 |
| Yes | 39 ( 27.7%) | 41 ( 29.5%) | 80 ( 28.6%) | |
| Previous Adefovir Therapy | | | | |
| No | 119 ( 84.4%) | 100 ( 71.9%) | 219 ( 78.2%) | 0.012 |
| Yes | 22 ( 15.6%) | 39 ( 28.1%) | 61 ( 21.8%) | |
| Duration of Previous Lamivudine Therapy (Days) | | | | |
| N | 140 | 139 | 279 | 0.098 |
| Mean (SD) | 1467.6 (846.52) | 1322.9 (849.54) | 1395.5 (849.60) | |
| Median | 1315.5 | 1162.0 | 1229.0 | |
| Q1, Q3 | 872.0, 1893.5 | 740.0, 1642.0 | 774.0, 1831.0 | |
| Min, Max | 238.0, 4538.0 | 48.0, 5825.0 | 48.0, 5825.0 | |
| Years Positive for HBV | | | | |
| N | 140 | 139 | 279 | 0.92 |
| Mean (SD) | 11.0 (8.21) | 10.5 (7.23) | 10.8 (7.73) | |
| Median | 8.3 | 8.5 | 8.4 | |
| Q1, Q3 | 4.8, 14.5 | 5.0, 14.3 | 4.9, 14.3 | |
| Min, Max | 1.2, 35.0 | 1.5, 34.9 | 1.2, 35.0 | |

BMI ($kg/m^2$) = [weight (kg)/height ($cm^2$)] × 10,000

Unknown, not recorded, or missing data was excluded from percentage calculations.

## Adherence

Adherence to study drugs was elevated in both treatment groups with a mean adherence rate around 98% and 99% of patients (i.e., all but 1 in the TDF and 2 in the TDF/FTC arms) reporting adherence ≥ 80%.

**Table 6.** GS-US-174-0121: Adherence to Study Drug (Safety Analysis Set)

| Adherence (%) Active | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| N | 141 | 139 | 280 |
| Mean (SD) | 98.7 (3.22) | 97.2 (10.33) | 98.0 (7.66) |
| Median | 99.7 | 99.9 | 99.8 |
| Q1, Q3 | 98.6, 100.0 | 98.6, 100.0 | 98.6, 100.0 |
| Min, Max | 66.7, 100.0 | 9.5, 100.0 | 9.5, 100.0 |

### Numbers analysed

The analysis sets used in this study for evaluation of efficacy and safety are described below:

**Table 7.** GS-US-174-0121: Analysis Set (Week 96)

| Analysis Set | TDF | FTC/TDF | Total |
|---|---|---|---|
| Randomized | 141 | 139 | 280 |
| Full Analysis Set (FAS) | 141 | 139 | 280 |
| Serologically Evaluable Analysis Set (HBeAg+ at baseline) | 65 | 68 | 133 |
| Biochemically Evaluable Analysis Set (ALT value above ULN at baseline) | 79 | 83 | 162 |
| Intensive PK Analysis Set | 41 | 38 | 79 |
| Safety Analysis Set | 141 | 139 | 280 |
| Modified Safety Analysis Set | 132 | 128 | 260 |

Source: Section 15.1, Tables 2.5, 2.8, 5.2, and 6.2; Appendix 16.2, Listings 1.4 and 2.3

## Outcomes and estimation

### Primary endpoint

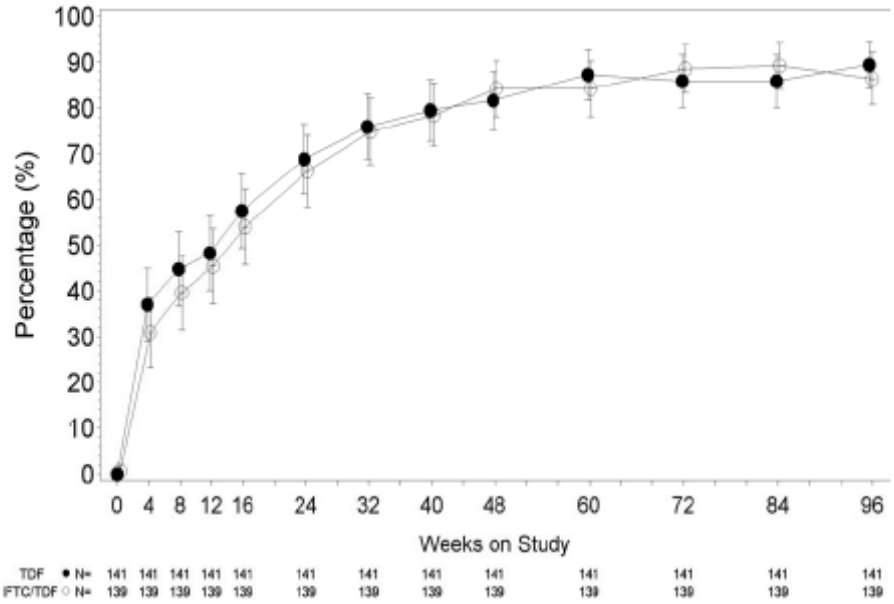
The primary efficacy endpoint for this study was the percentage of subjects with HBV DNA < 400 copies/mL at Week 96 (FAS, M=F analysis). Differences between the TDF and FTC/TDF treatment groups were evaluated using the CMH test, controlling for randomization strata (HBeAg status and ALT). Sensitivity analyses were performed for the primary efficacy endpoint to evaluate the difference between the TDF and FTC/TDF treatment groups using a large-sample normal approximation test of proportions.

**Table 8.**

| | TDF (N=141) | FTC/TDF (N=139) | Difference (TDF - FTC/TDF) | Standard Error Difference | 95% Confidence Interval | Z-score | p-value[a] | Stratified CMH p-value[b] |
|---|---|---|---|---|---|---|---|---|
| Missing = Failure | | | | | | | | |
| Week 96 | 126/141 (89.4%) | 120/139 (86.3%) | 3.0% | 3.9% | (-4.6%, 10.7%) | 0.78 | 0.44 | 0.43 |

At no time point through Week 96 with either the M=E or M=F analysis was there a statistically significant difference between the 2 treatment groups in the proportion of subjects with HBV DNA < 400 copies/mL. At Week 96, similar proportions of subjects in both treatment groups had HBV DNA < 400 copies/mL based on both the M=F and the M=E analyses (p > 0.43, CMH test).

**Figure 3.** GS-US-174-0121: GS-US-174-0121: Proportion of Subjects with HBV DNA < 400 copies/mL over Time (Full Analysis Set, M=F)



**All efficacy endpoints**

**Table 9.** GS-US-174-0121: Summary of Efficacy Endpoints at Week 96 (Full Analysis Set)

| Assessment (Week 96) | TDF | FTC/TDF | Overall | p-value |
|---|---|---|---|---|
| **HBV DNA, n (%)** | | | | |
| M=F | | | | |
| HBV DNA < 400 copies/mL (69 IU/mL) | 126/141 (89.4%) | 120/139 (86.3%) | 246/280 (87.9%) | 0.43 |
| HBV DNA < 169 copies/mL (29 IU/mL) | 121/141 (85.8%) | 116/139 (83.5%) | 237/280 (84.6%) | 0.58 |
| M=E | | | | |
| HBV DNA < 400 copies/mL (69 IU/mL) | 126/132 (95.5%) | 120/127 (94.5%) | 246/259 (95.0%) | 0.70 |
| HBV DNA < 169 copies/mL (29 IU/mL) | 121/132 (91.7%) | 116/127 (91.3%) | 237/259 (91.5%) | 0.92 |
| Confirmed Virologic Breakthrough[a] | 0/132 (0.0%) | 0/127 (0.0%) | 0/259 (0.0%) | – |
| Mean (SD) HBV DNA ($log_{10}$ copies/mL) | 2.29 (0.254) | 2.28 (0.241) | 2.28 (0.247) | – |
| Mean Change (SD) from Baseline in HBV DNA ($log_{10}$ copies/mL) | –4.16 (1.785) | –4.27 (1.916) | –4.21 (1.848) | 0.57 |
| HBV DNA < 400 copies/mL in Subgroups | | | | |
| Asian Subjects | 44/52 (84.6%) | 36/42 (85.7%) | 80/94 (85.1%) | 0.32[d] |
| Non-Asian Subjects | 82/89 (92.1%) | 84/97 (86.6%) | 166/186 (89.2%) | |
| HBeAg+ Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 16/18 (88.9%) | 13/17 (76.5%) | 29/35 (82.9%) | 0.80[d] |
| Subjects with ALT < 2 × ULN | 41/49 (83.7%) | 42/49 (85.7%) | 83/98 (84.7%) | |
| Total | 57/67 (85.1%) | 55/66 (83.3%) | 112/133 (84.2%) | |
| HBeAg– Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 16/16 (100.0%) | 15/16 (93.8%) | 31/32 (96.9%) | 0.20[d] |
| Subjects with ALT < 2 × ULN | 53/58 (91.4%) | 50/57 (87.7%) | 103/115 (89.6%) | |
| Total | 69/74 (93.2%) | 65/73 (89.0%) | 134/147 (91.2%) | |
| **ALT, n (%)** | | | | |
| M=F | | | | |
| Normal ALT | 99/141 (70.2%) | 97/139 (69.8%) | 196/280 (70.0%) | 0.94 |
| Normalized ALT[b] | 49/79 (62.0%) | 52/83 (62.7%) | 101/162 (62.3%) | 0.93 |
| M=E | | | | |
| Normal ALT | 99/130 (76.2%) | 97/122 (79.5%) | 196/252 (77.8%) | 0.52 |
| Normalized ALT[b] | 49/75 (65.3%) | 52/74 (70.3%) | 101/149 (67.8%) | 0.52 |
| Mean (SD) ALT (U/L) | 34.5 (SD 18.38) | 30.5 (SD 13.77) | 32.6 (SD 16.40) | – |
| Mean Change (SD) from Baseline in ALT | –38.2 (SD 92.91) | –60.5 (SD 154.88) | –49.0 (SD 126.98) | 0.10 |
| **Serology, n (%)[c]** | | | | |
| Confirmed HBeAg Loss | 10/65 (15.4%) | 9/68 (13.2%) | 19/133 (14.3%) | 0.72 |
| Confirmed Seroconversion to anti-HBe | 7/65 (10.8%) | 7/68 (10.3%) | 14/133 (10.5%) | 0.93 |
| Confirmed HBsAg Loss | 0/141 (0.0%) | 1/139 (0.7%) | 1/280 (0.4%) | 0.31 |
| Confirmed Seroconversion to anti-HBs | 0/141 (0.0%) | 0/139 (0.0%) | 0/280 (0.0%) | – |
| **Virology, n(%)** | | | | |
| Genotypic Change from Baseline at Conserved Sites Within the HBV Polymerase in Viremic Subjects at the Last Time Point Tested | 7/18 | 5/17 | 12/35[e] | – |

M=E: missing equals excluded, M=F: missing equals failure, SD: standard deviation, ULN: upper limit of the normal range
a Confirmed virologic breakthrough was defined as 2 consecutive 1.0-log10 or greater increases in serum HBV DNA from on-treatment nadir or 2 consecutive values ε 400 copies/mL after being < 400 copies/mL.
b Analysis included only subjects in the full analysis set (FAS) with baseline ALT above the ULN.
c For analysis of serological endpoints (HBeAg loss/seroconversion and HBsAg loss/seroconversion), only subjects who were antigen positive at baseline were included.
d P-values apply to the overall column.
e For 5 TDF subjects and 2 FTC/TDF subjects, the conserved-site changes were reversions toward consensus.

Only 1 subject (HBeAg-negative; genotype A; FTC/TDF group) in the study achieved HBsAg loss, which occurred at Week 16 and sustained through Week 96 while treatment was continued. This loss was not accompanied by seroconversion to antibody to HBsAg (anti-HBs). This result is comparable with other studies.

The virologic suppression and biochemical response (normal and normalized ALT) observed in the TDF group in this LAM-R study through Week 96 was generally consistent with that observed in two Phase 3 studies of TDF 300 mg in a non-LAM-R population (Studies GS-US-174-0102 and GS-US-174-0103) as summarized in Table below. It should be noted that subtle differences in the method for handling missing data in each study somewhat limits the comparison.

**Table 10.**

| Study | HBV DNA < 400 copies/mL n/N (%) | ALT Normal n/N (%) | ALT Normalized n/N (%) | HBeAg Loss n/N (%) | HBeAg Sero-conversion n/N (%) | HBsAg Loss n/N (%) | HBsAg Sero-conversion n/N (%) |
|---|---|---|---|---|---|---|---|
| GS-US-174-0121 | 126/141 (89%)[a,b] | 99/141 (70%)[a,b] | 49/79 (62%)[b,c] | 10/65 (15%)[b,d] | 7/65 (11%)[b,d] | 0 | 0 |
| GS-US-174-0102 | 216/240 (90%)[a,e] | 172/238 (72%)[a,e] | 159/225 (71%)[c,e] | HBeAg– population | HBeAg– population | 0 | 0 |
| GS-US-174-0103 | 128/168 (76%)[a,e] | 101/166 (61%)[a,e] | 96/160 (60%)[c,e] | 41/161 (26%)[d,e] | 36/161 (22%)[d,e] | 10/173 (6%)[a,e] | 8/173 (5%)[a,e] |

a Full analysis set was used (all subjects randomized and who received at least 1 dose of study drug).

b In this analysis subjects with missing values were considered as failures (M=F).

c The biochemically evaluable analysis set was used, which included only subjects with ALT above the upper limit of the normal range at baseline.

d The serologically evaluable analysis set was used, which included only subjects who were HBeAg positive (HBeAg+) at baseline.

e Algorithm for long-term evaluation, TDF, was used (LTE-TDF). In the LTE-TDF analysis, subjects discontinuing the study early and thus missing data due to death; safety, tolerability, or efficacy; loss to follow-up; or for any other reason with HBV DNA ≥ 400 copies/mL or an ongoing AE at the last on-study visit were considered failures. Subjects who added FTC to their TDF regimen were also considered failures in this analysis.

**Subgroup analysis**

Subgroup analyses were performed for HBV DNA endpoints by race (Asian subjects vs non-Asian subjects), and by randomization strata (ALT ≥2 xULN vs ALT < 2 xULN) for HBeAg+ and HBeAg- subjects, respectively.

**Table 11.** GS-US-174-0121: Analysis of HBV DNA < 400 copies/mL in Subgroups of Interest (Full Analysis Set, M=F)

| | TDF | FTC/TDF | Overall | p-value[a] |
|---|---|---|---|---|
| **Race** | | | | |
| **Week 48** | | | | |
| Asian Subjects | 42/52 (80.8%) | 38/42 (90.5%) | 80/94 (85.1%) | 0.48 |
| Non-Asian Subjects | 73/89 (82.0%) | 79/97 (81.4%) | 152/186 (81.7%) | |
| **Week 96** | | | | |
| Asian Subjects | 44/52 (84.6%) | 36/42 (85.7%) | 80/94 (85.1%) | 0.32 |
| Non-Asian Subjects | 82/89 (92.1%) | 84/97 (86.6%) | 166/186 (89.2%) | |
| **ALT Randomization Strata and HBeAg Status at Baseline** | | | | |
| **Week 48** | | | | |
| HBeAg+ Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 14/18 (77.8%) | 12/17 (70.6%) | 26/35 (74.3%) | 0.98 |
| Subjects with ALT < 2 × ULN | 34/49 (69.4%) | 39/49 (79.6%) | 73/98 (74.5%) | |
| Total | 48/67 (71.6%) | 51/66 (77.3%) | 99/133 (74.4%) | |
| HBeAg– Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 16/16 (100.0%) | 15/16 (93.8%) | 31/32 (96.9%) | 0.16 |
| Subjects with ALT < 2 × ULN | 51/58 (87.9%) | 51/57 (89.5%) | 102/115 (88.7%) | |
| Total | 67/74 (90.5%) | 66/73 (90.4%) | 133/147 (90.5%) | |
| **Week 96** | | | | |
| HBeAg+ Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 16/18 (88.9%) | 13/17 (76.5%) | 29/35 (82.9%) | 0.80 |
| Subjects with ALT < 2 × ULN | 41/49 (83.7%) | 42/49 (85.7%) | 83/98 (84.7%) | |
| Total | 57/67 (85.1%) | 55/66 (83.3%) | 112/133 (84.2%) | |
| HBeAg– Subjects | | | | |
| Subjects with ALT ≥ 2 × ULN | 16/16 (100.0%) | 15/16 (93.8%) | 31/32 (96.9%) | 0.20 |
| Subjects with ALT < 2 × ULN | 53/58 (91.4%) | 50/57 (87.7%) | 103/115 (89.6%) | |
| Total | 69/74 (93.2%) | 65/73 (89.0%) | 134/147 (91.2%) | |

CMH: Cochran Mantel-Haenszel, M=F: missing equals failure, ULN: upper limit of the normal range

a P-value based on a CMH test for the overall column.

**Resistance analysis**

- *Pretreatment genotypic analysis*

Viral genotyping was performed on baseline serum samples from all subjects, and the majority of subjects were found to have genotypes A–D. Genotype D virus was the most commonly observed genotype (44.7%).

Distribution of resistance mutation detected at screen (by INNO-LiPA) and baseline (population sequencing) is presented in the table below:

**Table 12.** Distribution of Resistance Mutations Detected at Screen (and Baseline by Treatment Arm)

| Category | HBV pol/RT Position | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|---|---|---|---|
| | | Number of Subjects with Changes detected by INNO-LiPA at Screen | | | Number of Subjects with Changes Detected by Population Sequencing at Baseline | | |
| Detectable ADV-R | rtA181T/V[a] | 3 | 3 | **6** | 1 | 4 | **5** |
| Detectable LAM-R | rtM204V/I | 139 | 139 | **278** | 125 | 128 | **253** |
| | rtL180M | 88 | 95 | **183** | 89 | 95 | **184** |
| | rtL80V/I | 64 | 68 | **132** | 46 | 51 | **97** |
| | rtV173L | 7 | 12 | **19** | 10 | 16 | **26** |
| Detectable ETV-R | rtT184A/I/S/L[b] | 6 | 9 | **15** | 7 | 9 | **16** |
| | rtM250I/L/V | 3 | 3 | **6** | 6 | 2 | **8** |
| | rtS202G | 3 | 1 | **4** | 1 | 0 | **1** |
| | rtI169T | NA[c] | NA | **NA** | 0 | 2 | **2** |

a Amino acids detectible by INNO-LiPA assay; A181C/G/S also detected by population sequencing

b Amino acids detected by population sequencing; INNO-LiPA assay was positive for either T184S/C/G/A or T184I/L/F/M

c NA = not available

Overall rtM204V/I was detected in 278 subjects by INNO-LiPA and in 253 subjects by population sequencing. The mutation rtL180M was seen in 183 or 184 subjects by INNO-LiPA or population sequencing. rtL80V/I was detected in more subjects by INNO-LiPA (132) than by population sequencing (97) and rtV173L was the least frequent LAM-R mutation detected in 19 and 26 subjects by INNO-LiPA or population sequencing respectively. In addition, mutations at the LAM/ADV-R position rtA181 were detected in a minority of subjects, 6 at screening and 5 at baseline.

- *Viral response in subjects with prior ADV exposure and/or ADV-R mutations at baseline*

Of the 280 subjects enrolled in Study 121, 61 were previously treated with ADV (17 subjects were enrolled despite having > 48 weeks of ADV treatment). Of these, 22 were in the TDF group and 39 were in the FTC/TDF group. In each group, the proportion of subjects with HBV DNA < 400 copies/mL at Week 96 was comparable for subjects with and without ADV exposure. In the TDF monotherapy group, 20/22 (90.9%) subjects with prior ADV exposure had HBV DNA < 400 copies/mL at Week 96 compared with 106/119 (89.1%) subjects without prior ADV exposure. In the FTC/TDF group, 33/39 (84.6%) subjects with prior ADV exposure had HBV DNA < 400 copies/mL at Week 96 compared with 87/100 (87%) subjects without prior ADV exposure.

Only 5 subjects had mutations detected at the ADV resistance (ADV-R) positions rtA181 and/or rtN236 at baseline. All 5 subjects had mutations at rtA181; no subject had any mutations detected at rtN236. Table 13 summarizes relevant clinical information for these subjects.

**Table 13.** GS-US-174-0121: HBV DNA Values at Baseline and Week 96 of Subjects with Adefovir Resistant Mutations at Baseline.

| Subject No. | ADV-R Mutation | Treatment Group | HBV DNA at Baseline[a] | HBV DNA at Week 96[a] |
|---|---|---|---|---|
| 4084 | rtA181A/S | FTC/TDF | 4.91 | 2.23 |
| 1032 | rtA181A/T | FTC/TDF | 7.38 | 2.23 |
| 2041 | rtA181C/G | FTC/TDF | 8.97 | 2.72 |
| 4028 | rtA181S | TDF | 3.79 | 2.23 |
| 2083 | rtA181T | FTC/TDF | 7.61 | 2.23 |

a HBV DNA expressed as $\log_{10}$ copies/mL

Four of the five subjects with ADV-R at baseline had HBV DNA < 400 copies/mL at Week 96, including the 1 subject on TDF monotherapy. Subject 2041 did not achieve HBV DNA < 400 copies/mL at Week 96; however, this subject had a high baseline HBV DNA level (8.97 log10 copies/mL), and had an HBV DNA decline of > 6.25 log10 by Week 96 with no evidence of virologic breakthrough (Week 96 HBV DNA value was 524 copies/mL).

- Impact of baseline HBV DNA level in ADV experienced patients

At baseline, 22/141 (15. 6%) and 39/139 (28.1%) of subjects in the TDF and FTC/TDF groups, respectively, had a history of ADV therapy in addition to documented LAM-R. The impact of baseline HBV DNA level (< 107 versus ≥ 107 copies/mL) on treatment response in this subgroup of subjects was further explored. Below is a summary of treatment responses by baseline viral load and by assigned treatment (Table 14). Regardless of the presence or absence of prior ADV experience, treatment responses were comparable between the 2 groups for those with low and high HBV DNA values at baseline.

As might be expected, the response rates overall at Week 96 in subjects with no exposure to ADV were not as robust in those with high baseline viral loads as those with lower viral loads (84.5% vs 91.4%, respectively); however, the opposite trend was observed in the small subgroup of subjects with high baseline viral load and prior ADV exposure. At Week 96, 90% of subjects with high baseline viral load and ADV experience had HBV DNA viral load < 400 copies/mL compared with 84.5% of subjects with high baseline viral load who were ADV-naive. A summary of the results is seen in Table 14 below.

Given these findings, the results suggest that there was no clinical difference in treatment response in the subgroup of subjects with prior ADV exposure, even when baseline viral load is considered.

**Table 14.** GS-US-174-0121: Number of Subjects With HBV DNA Viral Load <400 copies/mL at Week 96 by Baseline HBV DNA (<$10^7$ or ≥$10^7$ copies/mL) and ADV experience or Naïve (Missing=Failure)

| | Baseline HBV DNA < $10^7$ copies/mL | | | Baseline HBV DNA ≥ $10^7$ copies/mL | | |
|---|---|---|---|---|---|---|
| | TDF | FTC/TDF | Total | TDF | FTC/TDF | Total |
| ADV-Experienced Subjects | 15/16 (93.8%) | 20/25 (80.0%) | 35/41 (85.4%) | 5/6 (83.3%) | 13/14 (92.9%) | 18/20 (90.0%) |
| Non-ADV Experienced Subjects | 61/68 (89.7%) | 45/48 (93.8%) | 106/116 (91.4%) | 45/51 (88.2%) | 42/52 (80.8%) | 87/103 (84.5%) |
| Total | 76/84 (90.5%) | 65/73 (89.0%) | 141/157 (89.8%) | 50/57 (87.7%) | 55/66 (83.3%) | 105/123 (85.4%) |

- *Viral response in subjects with prior ETV exposure and/or ETV-R mutations at baseline*

Overall, 13 subjects (7 in the TDF group, 6 in the FTC/TDF group) were enrolled in Study 121 with previous exposure to ETV, despite prior ETV use being an exclusion criterion. Four of these subjects (2 in each treatment group) also had entecavir resistance (ETV-R) at baseline. Additionally, 21 subjects with no history of ETV exposure harboured ETV-R mutations at baseline. The presence of ETV-R in LAM-experienced, ETV-naïve subjects has been previously documented. In total, 34 subjects with either ETV exposure or ETV-R were enrolled in Study 121, 19 in the TDF group and 15 in the FTC/TDF group.

The percentage of subjects with ETV exposure and/or resistance who completed 96 weeks of treatment (30/34, 88.2%) was comparable to the overall study population (258/280, 92.1%).

In the TDF group, 16/19 (84.2%) subjects with ETV exposure and/or resistance completed 96 weeks of treatment compared with 117/122 (95.9%) subjects in the TDF group without ETV exposure and/or resistance (Fisher's exact test p-value = 0.075). In the FTC/TDF group, 14/15 (93.3%) of subjects with ETV exposure and/or resistance completed 96 weeks of treatment compared with 111/124 (89.5%) subjects in the FTC/TDF group without ETV exposure and/or resistance (Fisher's exact test p-value = 1.000).

In considering the mean HBV DNA and HBV DNA decline through Week 96 for subjects with or without ETV exposure and/or resistance at baseline, no significant differences were observed between groups, regardless of whether they were treated with TDF or FTC/TDF. The table below summarizes the mean viral load at baseline and Week 96, as well as the mean change in HBV DNA at W96 for all groups.

**Table 15.** GS-US-174-0121: Mean Viral Load at Baseline and Week 96 and Mean Change in HBV DNA at Week 96 by Entecavir Exposure or Resistance

| Category | Treatment Group | Number of Subjects at Baseline | Mean HBV DNA at Baseline[a] | Mean HBV DNA Week 96[a,b] | Week 96 HBV DNA Change from Baseline[a] |
|---|---|---|---|---|---|
| ETV Exposed | TDF | 7 | 6.69 | 2.57 | -4.12 |
| | FTC/TDF | 6 | 7.04 | 2.72 | -4.32 |
| No ETV Exposure | TDF | 134 | 6.39 | 2.27 | -4.16 |
| | FTC/TDF | 133 | 6.50 | 2.26 | -4.26 |
| ETV-R | TDF | 14 | 6.22 | 2.33 | -4.29 |
| | FTC/TDF | 11 | 6.76 | 2.43 | -4.53 |
| No ETV-R | TDF | 127 | 6.42 | 2.28 | -4.15 |
| | FTC/TDF | 128 | 6.50 | 2.27 | -4.24 |

a HBV DNA values expressed as $\log_{10}$ copies/mL

b 2.225 $\log_{10}$ copies/mL represents < 169 copies/mL

An additional analysis was performed to evaluate the proportion of subjects with HBV DNA < 400 copies/mL through Week 96. There was no significant difference observed between treatment groups at any study visit for subjects with ETV exposure and/or resistance. Furthermore, there was no significant difference in Week 96 response rates within the FTC/TDF treatment group, with 12/15 (80.0%) subjects with ETV exposure and/or resistance having HBV DNA < 400 copies/mL at Week 96, compared with 108/124 (87.1%) subjects without ETV exposure and/or resistance (Fisher's exact test p-value = 0.43). In the TDF group, subjects with ETV exposure and/or resistance had a lower rate of subjects with HBV DNA < 400 copies/mL at Week 96 (14/19, 73.7%) compared with subjects without ETV exposure and/or resistance (112/122 91.8%) (Fisher's exact test p-value = 0.03). This difference may be explained by the fact that in the TDF group, a lower percentage of subjects with ETV exposure and/or resistance (16/19, 84.2%) completed 96 weeks of treatment compared with subjects without ETV exposure and/or resistance (117/122 95.9%), despite this difference not reaching statistical significance (Fisher's exact test p-value = 0.075).

- *Resistance surveillance*

Clinical isolates were obtained for genotypic analysis from subjects who met the following criteria during the 96-week double-blind treatment period:

- Samples from subjects with HBV DNA ≥ 400 copies/mL (viremic) at Weeks 48 and 96 with or without virologic breakthrough. Virologic breakthrough was defined as 1.0 log10 copies/mL or greater (at least ten-fold) increases in HBV DNA from nadir, or values ≥ 400 copies/mL after being < 400 copies/mL while on study medication and confirmed after 2 consecutive values.
- Last on-study samples from viremic subjects who completed at least 24 weeks of treatment but discontinued prior to Week 96.

  In the TDF arm, genotypic analysis was conducted on 18 subjects at Year 1 and/or 2. In the FTC/TDF arm, genotypic analysis was conducted on 17 subjects at Year 1 and/or 2.

**Table 16.** GS-US-174-0121: Summary of Resistance Surveillance Conducted at Week 48 (Year 1) and Week 96 (Year 2) by Treatment

| | Week 48 | | | Week 96 | | |
|---|---|---|---|---|---|---|
| Category | TDF | FTC/TDF | Total | TDF | FTC/TDF | Total |
| Ongoing in the study (start of study or entered Year 2) | 141 | 139 | 280 | 134 | 132 | 266 |
| Discontinued prior to Week 24 | 5 | 3 | 8 | – | – | – |
| Discontinued at/after Week 24 and at/before Week 48 with HBV DNA < 400 copies/mL | 0 | 3 | 3 | – | – | – |
| Discontinued after Week 48 with HBV DNA < 400 copies/mL | – | – | – | 1 | 5 | 6 |
| HBV DNA < 400 copies/mL at Week 48 or Week 96 | 115 | 116 | 231 | 126 | 118 | 244 |
| HBV DNA data missing completely at random at Week 48 or Week 96 with HBV DNA < 400 copies/mL at flanking visits | 4 | 1 | 5 | 0 | 1 | 1 |
| **Resistance Surveillance** | | | | | | |
| Number of subjects included at Week 48, 96, or Last On-Treatment Visit with HBV DNA ≥ 400 copies/mL[a] | **17** | **16** | **33** | **7** | **8** | **15** |
| With confirmed virologic breakthrough | 0 | 2 | 2 | 0 | 0 | 0 |
| With unconfirmed virologic breakthrough | 0 | 1 | 1 | 0 | 2 | 2 |
| Without virologic breakthrough | 15 | 12 | 27 | 6 | 4 | 10 |
| Discontinued with confirmed virologic breakthrough | 1 | 0 | 1 | 0 | 0 | 0 |
| Discontinued with unconfirmed virologic breakthrough | 1 | 1 | 2 | 1[a] | 2 | 3 |

a The early discontinuation visit for Subject 1585-4036 was post Week 96; however, Subject 1585-4036 had no HBV DNA data after Week 84.

Of the 18 subjects who qualified for genotypic analysis in the TDF group at Week 48 and/or Week 96, three subjects discontinued prior to Week 96 (or had no HBV DNA data available after Week 84), 1 subject with confirmed virologic breakthrough and 2 subjects with unconfirmed virologic breakthrough. Of these, 1 subject had conserved and polymorphic site changes, 1 had no change from baseline, and 1 was unable to be genotyped.

The remaining 15 subjects were viremic (HBV DNA > 400 copies/mL) in the absence of virologic breakthrough at Week 48, with 6 subjects remaining viremic at Week 96. For these viremic subjects, HBV DNA levels generally declined from baseline to Week 48 and 96. Of the 15 viremic subjects, 7 had polymorphic and/or conserved-site changes in the HBV pol/RT at the last time of testing, 6 had no changes in the HBV pol/RT compared to baseline and 2 were unable to be genotyped.

**Table 17.** GS-US-174-0121: Viremic Subjects Randomized to TDF and Evaluated at Week 48 and Week 96

| Subjects Evaluated | Baseline HBV DNA[a] | Baseline pol/RT Conserved-Site Changes[b] | Evaluation Visit | HBV DNA at Time of Analysis[a] | Changes in pol/RT[b] |
|---|---|---|---|---|---|
| Subject who Discontinued with Confirmed Virologic Breakthrough | | | | | |
| 3999-4074 | 4.96 | **rtL77M, rtL180M, rtT184A, rtM204V** | Week 24 | 3.41 | **rtM180L rtA184T rtV204M** rtH248H/Q rtV266E/I/K/V rtK270K/T |
| Subjects who Discontinued with Unconfirmed Virologic Breakthrough | | | | | |
| 4029-2025 | 8.14 | **rtL180M, rtM204V** | Week 24 | 7.23 | No Change From BL |
| 1585-4036[c] | 5.57 | **None** | Week 84 | 2.65 | Unable to Genotype |
| Subjects without Virologic Breakthrough | | | | | |
| 2110-1016 | 9.38 | **rtL180M, rtM204V** | Week 48 | 2.73 | No Change From BL |
| 2088-1021 | 9.62 | **rtM204I** | Week 48 | 4.23 | **rtM171I/M** |
| 4766-1033 | 8.83 | **rtM204I** | Week 48 | 4.62 | rtE11E/K |
| | | | Week 96 | 3.93 | rtL13H, rtT16I rtK53N, rtS78T rtV80L, rtG110R rtS122F, **rtI204M** |
| 2088-1034 | 8.97 | **rtI169I/T, rtV173L, rtL180M, rtM204V, rtM250V** | Week 48 | 4.12 | **rtR153Q/R rtI/T169I rtP177P/S rtT184I/M/T rtV250M/V** |
| | | | Week 96 | 3.25 | Unable to Genotype |
| 2826-2003 | 7.73 | **rtL180L/M, rtM204I/M/V, rtI282V** | Week 48 | 3.02 | **rtL/M180L rtI/M/V204M** |
| 0342-2012 | 8.68 | **rtL180M, rtM204V** | Week 48 | 3.60 | No Change From BL |
| 4001-2013 | 8.97 | **rtL180M, rtM204V** | Week 48 | 3.30 | **rtV173L/V rtA194A/P** |
| | | | Week 96 | 3.01 | rtD131D/E **rtV173L/V rtM180L/M rtV204M/V** |

| Subjects Evaluated | Baseline HBV DNA[a] | Baseline pol/RT Conserved-Site Changes[b] | Evaluation Visit | HBV DNA at Time of Analysis[a] | Changes in pol/RT[b] |
|---|---|---|---|---|---|
| 2826-2019 | 8.41 | **rtV173L, rtL180M, rtM204V** | Week 48 | 3.70 | **rtH12H/R rtK275K/R rtR289Q/R** |
| 2826-2031 | 7.12 | **rtA87A/G, rtL180L/M, rtM204M/V** | Week 48 | 3.73 | **rtA/G87A rtN131T rtL132M rtL/M180L rtM/V204M** |
| | | | Week 96 | 3.21 | Unable to Genotype |
| 4845-2057 | 8.81 | **rtM204I** | Week 48 | 3.67 | No Change From BL |
| 2690-2076 | 8.97 | **rtV173L, rtL180M, rtM204V** | Week 48 | 4.51 | No Change From BL |
| 4029-2080 | 8.66 | **rtL180L/M, rtM204I** | Week 48 | 3.42 | **rtL/M180L** |
| 1069-2082 | 6.40 | **rtV173L, rtL180M, rtM204V** | Week 48 | 4.55 | No Change From BL |
| | | | Week 96 | 3.49 | No Change From BL |
| 2110-2094 | 8.89 | **rtL180M, rtM204V** | Week 48 | 4.54 | No Change From BL |
| | | | Week 96 | 3.49 | **rtS53I/S rtA219A/S** |
| 5713-4039 | 8.61 | **rtL180M, rtM204V** | Week 48 | 3.29 | No Change From BL |

a HBV DNA expressed in $\log_{10}$ copies/mL

b Conserved-site changes are shown in **BOLD**

c The early discontinuation visit for Subject 1585-4036 was post Week 96; however, Subject 1585-4036 had no HBV DNA data after Week 84.

Of the 17 subjects who qualified for genotypic analysis in the FTC/TDF group at Week 48 and/or Week 96, three subjects discontinued prior to Week 96, 1 with confirmed virologic breakthrough and 2 with unconfirmed virologic breakthrough. Of these, 1 subject had conserved-site changes while 2 had no change from baseline.

Three subjects had unconfirmed virologic breakthrough at their last evaluable time point, 2 with conserved and/or polymorphic-site changes and 1 was unable to be genotyped. The remaining 11 subjects were viremic (HBV DNA > 400 copies/mL) in the absence of virologic breakthrough at Week 48, with 4 subjects remaining viremic through Week 96. Of the 11 viremic subjects without breakthrough, 3 had polymorphic and/or conserved-site changes in the HBV pol/RT at the last time of testing. Seven subjects had no changes in the HBV pol/RT compared to baseline, and 1 subject was unable to be genotyped. The subject who could not be genotyped had no changes compared with baseline detected at an earlier time point.

**Table 18.** GS-US-174-0121: Viremic Subjects Randomized to the FTC/TDF Group Evaluated at Years 1 and 2

| Subjects Evaluated | Baseline HBV DNA[a] | Baseline pol/RT Conserved-Site Changes[b] | Evaluation Visit | HBV DNA at Time of Analysis[a] | Genotypic Analysis Results[b] |
|---|---|---|---|---|---|
| **Subjects Who Discontinued with Confirmed or Unconfirmed Virologic Breakthrough** | | | | | |
| 4037-2009 | 9.07 | **rtV173L, rtL180M, rtM204V** | Week 48 | 8.07 | **rtL173V rtM180L/M rtV204M/V** |
| 4035-2010 | 10.03 | **None** | Week 48 | 9.21 | No Change From Baseline |
| | | | Week 72 | 9.96 | No Change From Baseline |
| 4037-1013 | 8.69 | **rtL180M, rtA200A/V, rtM204V, rtI254I/L** | Week 96 | 2.67 | No Change From Baseline |
| **Subjects with Confirmed and/or Unconfirmed Virologic Breakthrough** | | | | | |
| 4037-1002 | 8.68 | **rtM204I** | Week 48 | 3.63 | **rtI80I/L rtI204I/M** rtC256C/S |
| 2038-1014 | 9.02 | **rtM204I** | Week 48 | 3.03 | Unable To Genotype |
| | | | Week 96 | 2.67 | Unable to Genotype |
| 4284-2090 | 7.05 | **rtL180M, rtM204V** | Week 48 | 3.03 | rtN337N/T |
| | | | Week 96 | 3.15 | rtN337N/T |
| **Subjects without Virologic Breakthrough** | | | | | |
| 2426-1007 | 8.75 | **rtL82L/M, rtM204I** | Week 48 | 3.72 | **rtH35H/R rtL/M82L** |
| 4284-1036 | 8.72 | **rtI169T, rtL180M, rtT184A/T, rtM204V** | Week 48 | 4.30 | No Change From RETEST |
| | | | Week 96 | 4.09 | No Change From RETEST |
| 2826-2004 | 6.63 | **rtM204I/M** | Week 48 | 3.13 | **rtI/V191V rtI/M204I** rtV207L/V |
| | | | Week 96 | 3.14 | **rtI/V191V rtI/M204I** rtV207L |

| Subjects Evaluated | Baseline HBV DNA[a] | Baseline pol/RT Conserved-Site Changes[b] | Evaluation Visit | HBV DNA at Time of Analysis[a] | Genotypic Analysis Results[b] |
|---|---|---|---|---|---|
| 2083-2041 | 8.97 | **rtK154Q, rtV173L, rtL180M, rtA181C/G, rtM204V, rtR343K** | Week 48 | 3.84 | No Change From Baseline |
| | | | Week 96 | 2.72 | Unable to Genotype |
| 2865-2049 | 8.94 | **rtL180M, rtA200A/V, rtM204V** | Week 48 | 3.77 | No Change From Baseline |
| 4760-2067 | 8.72 | **rtV173L, rtL180M, rtM204V** | Week 48 | 3.22 | No Change From Baseline |
| 5248-2074 | 10.12 | **None** | Week 48 | 3.54 | No Change From Baseline |
| 4284-2091 | 8.70 | **rtI169T, rtL180M, rtT184A, rtM204V** | Week 48 | 3.57 | No Change From RETEST |
| 1474-4005 | 8.99 | **rtM204I** | Week 48 | 3.95 | **rtV23I/V** |
| 1932-4081 | 8.61 | **rtL180M, rtM204V** | Week 48 | 4.24 | rtI266I/M |
| | | | Week 96 | 3.57 | No Change From Baseline |
| 4766-4098 | 8.90 | **rtV173L, rtL180M, rtM204V** | Week 48 | 3.58 | No Change From Baseline |

a HBV DNA expressed in $\log_{10}$ copies/mL

b Conserved-site changes are shown in **BOLD**.

No ADV resistance-associated mutation was detected in any of the patients who qualified for genotypic evaluation.

Based on these data, no subjects showed genotypic resistance to TDF through Week 96.

Phenotypic evaluations were performed for 4 subjects (3 in the TDF group and 1 in the FTC/TDF group) who developed changes at conserved sites at Week 48 and did not subsequently suppress HBV DNA to < 400 copies/mL by Week 96. None of the isolates containing conserved-site changes in the HBV pol/RT conferred reduced susceptibility to TFV.

**Table 19.** Phenotypic Evaluation of Qualified Subjects on TDF Therapy

| Isolate | Baseline and Changes from Baseline in HBV pol/RT | $EC_{50}$ (μM) | Fold Change[a] | $EC_{50}$ (μM) | Fold Change[a] |
|---|---|---|---|---|---|
| | | Tenofovir | | FTC | |
| 2004 – BL | **rtM204I/M** | 14.6 ± 7.3 | 1.0 | 16.0 ± 6.9 | 1.0 |
| 2004 – Week 48 | **rtI/V191V rtI/M204I** rtV207L/V | 15.2 ± 3.4 | 1.0 | >200 | >12.5 |
| 2004 – Week 48 – Clone 2 | **rtM204I**, rtV207L | 14.0 ± 7.2 | 1.0 | >200 | >12.5 |
| 2013 – BL | **rtL180M, rtM204V**[b] | 15.8 ± 5.9 | 1.0 | ND[c] | ND |
| 2013 – Week 48 | **rtV173L/V rtA194A/P** | 22.2 ± 10.9 | 1.4 | ND | ND |
| 2013 - Week 48 – Clone 5 | **rtA194P** | 18.0 ± 7.5 | 1.1 | ND | ND |
| 1034 - BL | **rtI169I/T, rtV173L rtL180M, rtM204V**[b] **rtM250V** | 11.7 ± 5.5 | 1.0 | ND | ND |
| 1034 - Week 48 | rtR153Q/R, **rtI/T169I rtP177P/S rtT184I/M/T rtV250M/V** | 11.9 ± 2.8 | 1.0 | ND | ND |
| 1034 - Week 48 – Clone 1 | **rtT184M** | 11.5 ± 1.5 | 1.0 | ND | ND |
| 1034 - pCMVHBV – SDM Clone 1 | **rtP177S** | 12.3 ± 5.8 | 1.3 | ND | ND |
| 2031 – BL | **rtA87A/G rtL180L/M rtM204M/V** | 10.5 ± 6.1 | 1.0 | ND | ND |
| 2031 – Week 48 | **rtA/G87A**, rtN131T **rtL132M**, **rtL/M180L rtM/V204M** | 14.9 ± 6.6 | 1.4 | ND | ND |
| | | Controls | | | |
| pHY92 | Wild-type | 10.5 ± 5.1 | 1.0 | 8.5 ± 4.5 | 1.0 |
| ADV-R | rtA181V+rtN236T | 45.1 ± 21.7 | 4.3 | ND | ND |
| LAM-R | rtL180M, M204V | ND | ND | >200 | >23.5 |
| pCMVHBV | Wild-type | 9.4 ± 3.2 | 1.0 | ND | ND |

a Defined as the $EC_{50}$ of the last on treatment sample/$EC_{50}$ of BL sample. A value < 2-fold is within assay variability

b Baseline LAM resistance mutations were maintained through Week 48

c ND = Not determined

**PK Sub-study**

Subjects with CLcr between 50 to 80 mL/min at study entry were included in a PK substudy. These assessments were done once, during a single clinic visit occurring on or after Week 4 of study participation to ensure subjects were at steady state. It was anticipated that a minimum of 30 and a maximum of 50 subjects would meet the criteria for participation in the PK substudy (ie, screening CLcr 50 to 80 mL/min).

Of the 280 subjects randomized to receive of TDF or FTC/TDF in the study, 78 subjects were included in the intensive PK substudy analysis set. Of these, 38 subjects received FTC/TDF and 41 subjects received TDF.

Plasma was collected at time 0 (pre-dose), and at 1, 2, 4, 6, and 8 hours post-dose at a single clinic visit at Week 4 or anytime thereafter. Subjects were instructed to take their daily dose of study medication at the same time as the time 0 hour PK sample (e.g. 8:00 am) for at least 2 days prior to the visit. Additional details have been provided.

In addition to the PK substudy described above, all subjects who experienced a CLcr decrease to < 50 mL/min during the study were required to have this value confirmed within 72 hours (or alternatively, a 24-hour urine for CLcr could have been measured in lieu of a calculated CLcr). If the CLcr was confirmed to have been < 50 but ≥ 30 mL/min, the dosing interval was adjusted to every 48 hours. Subjects were then instructed to return to the clinic 1 week after the commencement of the dose adjustment to have a full PK profile performed. This was performed to ensure, retrospectively, that study drug levels (TFV) were maintained within an acceptable therapeutic range. The procedures were identical to those of the PK substudy with the exception that additional time points were included as noted below.

Plasma samples were collected at least 1 week after the start of every-other-day dosing at: 0 (pre-dose), 1, 2, 4, 6, 8, 24, and 48 hours post-dose. Subjects were instructed to take their every-other-day dose of study drug at the same time as the 0 hour PK sample (e.g. 8:00 am).

All subjects with confirmed CLcr of < 30 mL/min were to have been discontinued from the study.

Concentrations of tenofovir (TFV) in plasma samples were determined using a fully validated LC-MS/MS bioanalytical method. All samples were analyzed in the timeframe supported by frozen stability storage data. Assay validation parameters are summarized in the table below.

**Table 20.**

| Parameter | TFV |
|---|---|
| Linear range (ng/mL) | 5–3000 |
| LLQ[a] (ng/mL) | 5 |
| Interassay precision range[a] | 2.4%–6.5% |
| Interassay accuracy range | –4.7%–2.0% |
| Stability in frozen matrix (days) | 190 days at –20°C and –70°C |

Source: Appendix 16.1.10

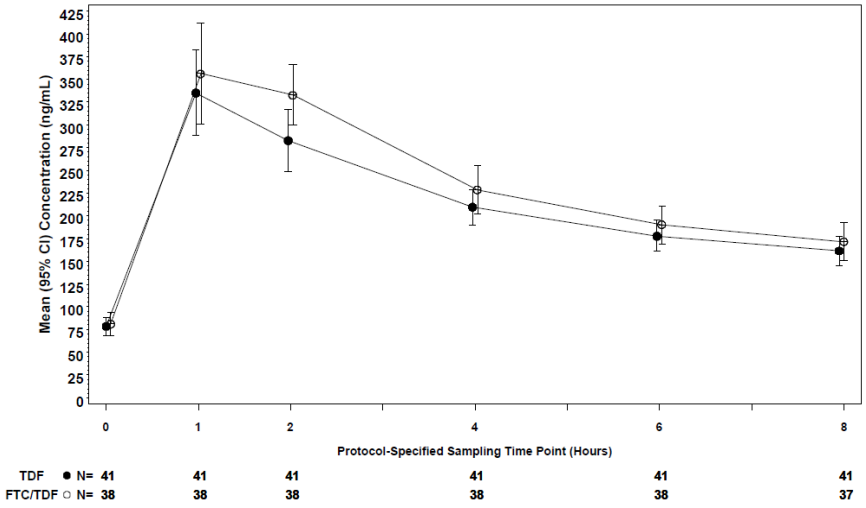
Steady-state tenofovir (TFV) PK parameters ($C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, and $AUC_{tau}$) were estimated by application of a nonlinear curve-fitting software WinNonlin® using non-compartmental method. The non-compartmental method employed Model 200 in conjunction with the linear up/log down trapezoidal rule.

Intensive PK sampling was conducted at steady state (at Week 4 or any time thereafter). However, samples were collected up to 8 hours post-dose only. The zero (pre-dose [$C_{0h}$]) time point was used as a surrogate for the 24-hour post-dose ($C_{24h}$) time point for purposes of estimating $AUC_{tau}$. Due to limited sampling duration, steady-state $t_{1/2}$ could not be reliably estimated and therefore is not presented.

- Results

Mean (± SD) plasma concentration–time linear plots for TFV following administration of TDF or FTC/TDF in subjects with $CL_{cr}$ 50 to 80 mL/min are shown in below figure.

**Figure 4.**




Tenofovir exposure parameters ($AUC_{tau}$ and $C_{max}$) were similar following administration of TDF or FTC/TDF 200/300 mg.

**Table 21.** GS-US-174-0121: Statistical Comparison of Tenofovir Pharmacokinetic Parameters for Test Versus Reference Treatments (Intensive PK Analysis Set)

| Tenofovir PK Parameter | Geometric Least Squares Means | | Geometric Least Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test Treatment | Reference Treatment | | |
| FTC/TDF 200/300 mg (Test) vs TDF 300 (Reference) | N = 38 | N = 41 | | |
| $AUC_{tau}$ (ng•h/mL) | 3655.1 | 3305.8 | 1.11 | (0.99,1.24) |
| $C_{max}$ (ng/mL) | 406.9 | 349.3 | 1.16 | (1.00, 1.35) |
| $C_{0h}$ (ng/mL) | 75.0 | 72.0 | 1.04 | (0.89,1.21) |

As TFV exposures were similar following administration of TDF or FTC/TDF, the TFV PK parameters all HBV subjects with CLcr 50 to 80 mL/min receiving TDF or FTC/TDF were pooled for comparison purposes.

The summary of TFV exposures in all subjects is presented below:

**Table 22.** GS-US-174-0121: Summary of TFV Exposures (TDF Alone or with FTC) in HBV Subjects with Creatinine Clearance 50−80 mL/min

| Tenofovir PK Parameter | TDF 300 mg or FTC/TDF 200/300 mg (N = 79) |
|---|---|
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 3631.8 (31.6) |
| $C_{max}$ (ng/mL) Mean(%CV) | 402.2 (32.6) |
| $C_{0h}$ (ng/mL) Mean (%CV) | 79.8 (45.7) |

Note: The zero (predose [$C_{0h}$]) time point was used as a surrogate for the 24 hours postdose ($C_{24h}$) time point for purposes of estimating $AUC_{tau}$.

According to the MAH, those data are consistent with historical data in subjects with normal renal function (GS-01-929 and GS-01-932), suggesting that TFV PK is not affected in subjects with mild renal impairment.

Subjects whose CLcr decreased to < 50 but ≥ 30 mL/min were dose adjusted by increasing the dosing interval to every 48 hours. Although based on a limited sample size (n = 7), the TFV exposures following dose adjustment in subjects with CLcr < 50 but ≥ 30 mL/min were in the range of those observed with subjects with CLcr 50 to 80 mL/min receiving once daily treatment.

**Table 23.** GS-US-174-0121: Summary of TFV Exposures (TDF Alone or with FTC) in HBV Subjects with Dose Adjustment (Creatinine Clearance 30−49 mL/min)

| Tenofovir PK Parameter[a] | TDF 300 mg or FTC/TDF 200/300 mg (N = 7) |
|---|---|
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 4511.8 (22.8) |
| $C_{max}$ (ng/mL) Mean (%CV) | 415.0 (35.5) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 32.0 (32.1) |

[a] Summary statistics based on 7 intensive PK profiles collected following dose adjustments in 6 subjects.

## Ancillary analyses

### Cirrhotic patients

Liver histology was not required for patients entering Study 121 and non-invasive methods for assessing fibrosis were also not employed, making identification of cirrhotic subjects challenging. Seven (2.5%) subjects were identified as having a diagnosis of cirrhosis based on medical history, 4 (2.8%) in the TDF group and 3 (2.1%) in the FTC/TDF group. There were 2 additional subjects, both in the FTC/TDF treatment group, who were diagnosed with hepatocellular carcinoma (HCC) during the study. One of these subjects with HCC (No. 4037-1013) was noted to be cirrhotic at the time of a serious adverse event (SAE) for sepsis, intra-abdominal infection, and diarrhea, while the other subject (No. 1591-4056) was noted by his treating physician to have possibly transitioned to cirrhosis at the time of the SAE of HCC.

Overall, the treatment responses in these 9 (3.2%) subjects were excellent, in all but 1 instance (Subject 4037-1013 having the highest baseline HBV DNA level [Table 24]); full HBV DNA suppression

was achieved with values below the lower limit of assay detection (< 169 copies/mL or 2.225 log10 copies/mL). A summary of efficacy results for these subjects is shown in Table 24.

**Table 24.** GS-US-174-0121: Efficacy Results of Subjects with Diagnosis of Cirrhosis Prior Study or HCC During the Study

| Subject No. | Treatment Group | Baseline HBV DNA ($log_{10}$ copies/mL) | Week 96 HBV DNA ($log_{10}$ copies/mL) Response[a] |
|---|---|---|---|
| 2690-1010[b] | TDF | 7.62 | 2.23 |
| 4530-2051[b] | TDF | 4.62 | 2.23 |
| 4530-4102[b] | TDF | 5.21 | 2.23 |
| 4763-3028[b] | TDF | 8.07 | 2.23 |
| 0342-1006[b] | FTC/TDF | 8.44 | 2.23 |
| 1591-4017[b] | FTC/TDF | 4.25 | 2.23 |
| 1591-4069[b] | FTC/TDF | 4.24 | 2.23 |
| 4037-1013[c] | FTC/TDF | 8.69 | 2.67 (471 copies/mL) |
| 1591-4056[c] | FTC/TDF | 2. 99 | 2.23 |

a For values < 169 copies/mL, the $log_{10}$ result was set at 2.23
b Diagnosis of cirrhosis based on medical history
c Diagnosed with hepatocellular carcinoma during study

In summary, in the 9 subjects with known cirrhosis participating in Study 121, treatment efficacy was similar to the overall population.

## Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 25.** Summary of Efficacy for trial

| **Title:** | **A Phase 3b, Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects with Chronic Hepatitis B who are Resistant to Lamivudine** | |
|---|---|---|
| Study identifier | GS-US-174-0121 | |
| Design | Randomized (throughout 240 weeks), Double-Blind, Double-Dummy | |
| | Duration of main phase:<br>Duration of run-in phase:<br>Duration of extension phase: | 96 weeks<br>Not applicable<br>240 weeks |
| Hypothesis | Superiority | |
| Treatment groups | TDF | One tablet containing tenofovir disoproxil fumarate (TDF) 300 mg or matching placebo. Up to 240 weeks, n=141. |

| | | | |
|---|---|---|---|
| | TDF / FTC | | One tablet containing tenofovir disoproxil fumarate (TDF) 300 mg and 200 mg emtricitabine (FTC) or matching placebo. Up to 240 weeks, n=139. |
| Endpoints and definitions | Primary endpoint | HBV DNA | Proportion of subjects with HBV DNA < 400 copies/mL (69 IU/mL) at Week 96 was summarised. |
| | Secondary | HBV DNA-169 | Proportion of subjects with HBV DNA < 169 copies/mL (29 IU/mL) at Week 96 was summarised. |
| | Secondary | Virologic breakthrough | Proportion of subjects with confirmed virologic breakthrough through to Week 96 was summarised. Confirmed virologic breakthrough was defined as 2 consecutive 1.0-log10 or greater increases in serum HBV DNA from on-treatment nadir or 2 consecutive values ≥ 400 copies/mL after being < 400 copies/mL. |
| | Secondary | Change from Baseline in HBV DNA | Mean HBV DNA and mean change from baseline in HBV DNA were summarized at Week 96. |
| | Secondary | Normal ALT | The proportion of subjects with ALT within the normal range at Week 96 was summarised. |
| | Secondary | Normalized ALT | The proportion of subjects with baseline ALT above the ULN but within the normal range at Week 96 was analyzed. |
| | Secondary | Change from Baseline in ALT | Mean ALT and mean change from baseline in ALT were summarized at Week 96. |
| | Secondary | HBV Serology: HBeAg loss / seroconversion | Proportion of subjects who were HBeAg positive at Baseline and who had HBeAg loss was summarized at Week 96. Loss of HBeAg was defined as a change of detectable HBeAg from positive to negative. Proportion of subjects who were HBeAg positive at Baseline and who had seroconversion to antibody against HBeAg was summarized at Week 96. Seroconversion to anti-HBe was defined as a change of detectable antibody to HBeAg from negative to positive. |
| | Secondary | HBV Serology: HBsAg loss / seroconversion | Proportion of subjects who had HBsAg loss was summarized at Week 96. Loss of HBsAg was defined as change of detectable HBsAg from positive to negative. Proportion of subjects who had seroconversion to antibody against HBsAg was summarized at Week 96. Seroconversion to anti-HBs was defined as a change of detectable antibody to HBsAg from negative to positive. |

| | | | |
|---|---|---|---|
| Database lock | 16 February 2012 | | |
| **Results and analysis** | | | |
| **Analysis description** | **Primary analysis** | | |
| Analysis population and time point description | Intent to treat (missing = failure) | | |
| Descriptive statistics and estimate variability | Treatment group | TDF | TDF / FTC |
| | Number of subjects | 141 | 139 |
| | HBV DNA (%) | 89.4 | 86.3 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | 3.1 |
| | | Standard error of difference (%) | 3.9 |
| | | P-value | 0.43 |
| **Analysis description** | **Secondary analyses** | | |
| Analysis population and time point description | Intent to treat (missing = failure) | | |
| Descriptive statistics and estimate variability | Treatment group | TDF | TDF / FTC |
| | Number of subjects | 141 | 139 |
| | HBV DNA-169 (%) | 85.8 | 83.5 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | 2.3 |
| | | P-value | 0.58 |
| | Virologic breakthrough (n) | 3 | 4 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | Difference, n | 1 |
| | | P-value | - |
| | Change from Baseline in HBV DNA ($log_{10}$ copies/mL) | -4.16 | -4.27 |
| | Standard Error | 1.785 | 1.916 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | Difference | 0.11 |
| | | P-value | 0.57 |

| | | | |
|---|---|---|---|
| | Normal ALT (%) | 70.2 | 69.8 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | 0.4 |
| | | P-value | 0.94 |
| | Normalized ALT (%) | 62.0 | 62.7 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | -0.7 |
| | | P-value | 0.93 |
| | Change from Baseline in ALT (U/L) | -38.2 | -60.5 |
| | Standard deviation | 92.91 | 154.88 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | Difference | 22.3 |
| | | P-value | 0.10 |
| | HBV Serology: HBeAg loss / seroconversion (%) | 15.4 / 10.8 | 13.2 / 10.3 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | 2.2 / 0.5 |
| | | P-value | 0.72 / 0.93 |
| | HBV Serology: HBsAg loss / seroconversion (%) | 0.0 / 0.0 | 0.7 / 0.0 |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | TDF vs TDF / FTC |
| | | % difference | 0.7 / 0.0 |
| | | P-value | 0.31 / - |

### 1.4.2. Discussion on clinical efficacy

## Design and conduct of clinical study

Ongoing study GS-US-174-0121 compares the efficacy and safety of TDF monotherapy with FTC/TDF combination therapy in the treatment of subjects with CHB who, at the time of screening, were receiving LAM and who had documented LAM-R mutations (rtM204V/I with or without rtL180M). A total of 240 weeks of blinded treatment are planned; the report provided in this submission summarizes the results through Week 96 as the basis to extend the indication for Viread to patients with LAM-R.

The study population was a mixed population of patients with HBeAg positive or negative disease. Patients should have confirmation of HBV pol/RT mutation(s) known to confer resistance to LAM (rtM204I/V +/- rtL180M) as determined by hybridization-based assay (INNO LiPA).

To be included, patients should have baseline HBV DNA level ≥ 3 log10 IU/mL. The HBV DNA entry threshold was reduced through 2 protocol amendments from 5 log10 copies/ml to 4 log10 copies/ml

and then 3 log10 IU//ml to be more consistent with current standard of treatment. Viral load rapidly increases in these patients and an early intervention would be crucial to prevent the occurrence of hepatitis flares and hepatic decompensation. Therefore, such modification is considered acceptable.

Likely due the fact that TDF has some degree of cross-resistance with ADV, prior or current ADV treatment (inclusive of ADV+LAM) was allowed if ≤ 48 weeks. However, presence of resistance to ADV was not an exclusion criteria.

TDF+FTC combination was used as comparator in this study, which is endorsed. TDF+FTC combination therapy is not approved for the treatment of patients with CHB, despite used in this setting in clinical practice. As a matter of fact, use of the convenient single tablet FTC/TDF in CHB patients is supported by therapeutic guidelines, notably by the EASL guideline. It is agreed that ETV monotherapy is not an optimal option for the management of patients with LAM-R due to the cross-resistance profile of the drugs. Other comparators might have been used such as ADV+LAM combination therapy or TDF+LAM combination therapy. However, given that TDF is known to be superior to ADV (moreover, literature data suggest add-on combination therapy with ADV+LAM is an effective therapy but only when initiated during the early stages of resistance development) and considering that FTC is a lamivudine–like agent, the choice of the fixed-dose combination FTC/TDF in this study is endorsed.

The primary endpoint was HBV DNA < 400 copies/ml at week 96 (HBV DNA <169 copies/ml was included among secondary endpoints). Virological suppression has been fully recognised as a surrogate marker of treatment efficacy and sustained reduction of HBV DNA levels are associated with improved prognosis. Satisfactorily, biochemichal and serological endpoints are amongst secondary endpoints. No liver biopsy was performed in the study and indeed liver biopsy is not mandatory when deciding treatment management of patients with LAM-R. Moreover, correlation between viral suppression and histological improvement is now well documented (notably established for TDF by the 5 years histological data from pivotal studies -102/-103).

Randomization was stratified by HBeAg status and ALT level (< or ≥ 2 ULN). HBeAg + and - diseases are two distinct disease with different response to therapy and HBeAg status is a well-endorsed stratification factor. Since there were no requirements as regards ALT level at screening and it is anticipated that a substantial number of patients would have normal ALT value since currently under therapy, stratification according to ALT level seems appropriate. Moreover, this factor might help ensure balanced repartition of patients who entered in the study following breakthrough or with partial response to prior treatment.

Of note, analysis of the primary endpoint was modified per protocol amendment 4 to occur at Week 96 and was not to be conducted using group sequential testing annually (ie, every 48 weeks). A single comparison at a longer time-point is considered relevant and this change in primary endpoint is not anticipated to have significantly impacted statistical analysis.

A high screen failure rate (62%) was reported in the study. The MAH provided major reasons for screen failure in the study (i.e. lack of documented LAM-R and/or not receiving current treatment with LAM, or insufficient HBV DNA level). Length of exposure to ADV did not account for important reason for screen failure while it could have been expected as a limiting factor for enrolment given that longer than 48 weeks pre-treatment with ADV could be observed in practice.

## Efficacy data and additional analyses

A total of 280 patients were randomized and treated (141 subjects received TDF once daily and 139 subjects received FTC/TDF once daily).

A total of 258 subjects (94.3% of subjects [133/141] in the TDF group and 89.9% of subjects [125/139] in the FTC/TDF group) completed the study through Week 96.

Baseline characteristics of patients were similar in both groups but with the exception of prior ADV treatment. Almost twice as many patients received prior treatment with ADV in the FTC/TDF group compared with the TDF group (28.1% vs 15.6%). The level of HBV DNA at the beginning of TDF treatment in ADV resistant patients is considered a factor that could have an influence in the probability of complete virologic response. However, the data presented, provide reassurance that baseline viral load and prior ADV-experienced did not significantly impact response to TDF in this study. Indeed, high rate of virological suppression ($\geq$ 80% having < 400 copies/ml) were reported in ADV-experienced and non ADV-experienced patients as well as in patients with high viral load or low viral load receiving TDF. Although based on small sample sizes, there is no obvious evidence that these factors may significantly reduce the likelihood of response. There is also no apparent advantage of FTC/TDF combination therapy over TDF in the subgroups, even though it is noted that in the likely harder-to-treat population of ADV-experienced patients with high viral load, FTC/TDF provided a higher, albeit a non-significant increased responder rate.

Of note, enrolment of compensated cirrhotic was allowed per amendment 3. It was shown that in the 9 patients with known cirrhosis participating in Study 121, treatment efficacy was similar to the overall population.

Results for the primary endpoint (proportion of subjects with HBV DNA < 400 copies/mL (69 IU/mL) at week 96) show that 89.4% (126/141) of subjects in the TDF group and 86.3% (120/139) of subjects in the FTC/TDF group met the primary efficacy endpoint. When a more stringent criteria is used (proportion of patients with HBV DNA <169 copies/ml) the results are quite similar (85.8% of subjects in the TDF group and 83.5% of subjects in the FTC/TDF group). HBV DNA levels declined over the study period with similar mean changes from baseline in both groups (mean change from baseline in HBV DNA in the TDF group was −4.16 log10 copies/mL and in the FTC/TDF group was −4.27 log10 copies/mL). These results are consistent with what has been observed in previous studies in HBV infected adults. As previously observed in HBV infected adults, the high virological potency of TDF does not translate into high rate of HBeAg or HBsAg seroconversion. Although the mechanism is unclear, the literature is consistent in reporting from prospective, randomized, controlled trials that the rate of hepatitis B e antigen seroconversion is lower in patients with LAM-R HBV compared with treatment-naive patients, regardless of the rescue regimen employed. Moreover, only 1 patient achieved Hbs Ag loss without seroconversion to anti-HBs, which is however comparable with other published data. HBeAg and HBsAg loss and seroconversion will be further monitored throughout the remainder of the study period.

Around 40% of patients in both groups had ALT levels within the normal range at baseline. This is consistent with the target population, as salvage therapy should be initiated at the time of virologic breakthrough, prior to the biochemical breakthrough. As expected, a clear benefit in both treatments was also demonstrated for the biochemical response [the percentage of subjects with normal ALT at week 96 increased to around 70 % (in both groups)].

Based on the resistance surveillance and genotypic analysis data, no subjects showed genotypic resistance to TDF through Week 96. Proportion of viral breakthrough was low and no clear pattern of mutations to TDF was found.

Overall, a clear benefit of TDF monotherapy in patients with lamivudine resistance has been demonstrated in this study. However due to small numbers involved, the available data (week 96 results) cannot clarify whether TDF+FTC would not be more beneficial than TDF monotherapy in patients having pejorative criteria (such as high viral load, prior ADV experience, with or without rtA181T resistance mutation, prior ETV exposure).

The proposed indication by the MAH reflects the populations studied in respective supportive studies. The indication was restricted to patients with compensated CHB and evidence of LAM-R virus. The CHMP considers that tenofovir should be indicated in patients with LAM-R regardless of whether they have compensated or decompensated CHB. Indeed, although there is limited experience in patients with both lamivudine-resistant CHB and decompensated liver disease, (study GS-US-174-0121 was conducted in patients with LAM-R and compensated CHB and few patients with evidence of LAM-R were included in study GS-US-174-0108 in patients with decompensated CHB), the high potency and high genetic barrier of TDF as well as the lack of cross-resistance between TDF and LAM, make the extrapolation adequate. Viread is considered as the standard of care for patients with LAM-R in both situations.

### 1.4.3. Conclusions on the clinical efficacy

As the basis to extend the indication for Viread to CHB patients with LAM-R, the MAH submitted the 96 weeks report of the study GS-US-174-0121 that compares the efficacy and safety of TDF monotherapy versus FTC/TDF combination therapy in patients with CHB who, at the time of screening, were receiving LAM and who had documented LAM-R mutations (rtM204V/I with or without rtL180M). The study was designed to answer the question whether TDF alone is as effective as TDF+FTC to manage patients with lamivudine resistance. The study is still ongoing and will provide blinded comparison of the two strategies over 240 weeks.

Overall, the study design can be considered as adequate. At week 96, a similarly high proportion of patients achieved viral suppression in both treatment groups (TDF: 89.4% vs TDF/FTC: 86.3%). Viral potency is also observed with the most stringent criterion of HBV DNA <169 copies/ml and comparable results were observed between both treatments arms at week 96 on all (virological, biochemical and serological) endpoints.

Those results confirm that TDF is highly effective in patients with LAM-R. The CHMP nevertheless highlights the limitation notably as regards the potential advantage of FTC/TDF over TDF in patients having pejorative factors. Indeed, taking account of limited sample size, the available data (week 96 results) cannot clarify whether TDF+FTC would not be more beneficial than TDF monotherapy in patients having pejorative criteria (such as high viral load, prior ADV experience, with or without rtA181T resistance mutation, prior ETV exposure).

Even though patients with decompensated CHB were not specifically enrolled in this study in LAM-R, it is considered that due to its high potency and genetic barrier, the lack of cross-resistance between TDF and LAM and in view of the clinical experience already gained in decompensated patients (study GS-US-174-0108), tenofovir is also a valid option in patients with LAM-R and decompensated CHB.

## *1.5. Clinical safety*

### 1.5.1. Introduction

The salient aspect of the safety profile of TDF relies on its renal and bone toxicity.

Long-term data in CHB are currently available from the open-label extension phase of studies 102&103 consisting of treatment with TDF up to 384 weeks (Year 8).

Cumulative worldwide exposure to TDF or TDF-containing products since first marketing approval in the US on 26 October 2001 to 31 May 2012 is estimated to be around 5 million patients-years of treatment.

The principal clinical safety data for TDF in subjects with CHB who are resistant to LAM are derived from on-going, long-term, Phase 3b clinical study sponsored by Gilead Sciences, GS-US-174-0121. The safety analysis set (primary analysis set for the Week 96 safety interim analysis) includes 141 subjects who received TDF 300 mg and 139 subjects who received FTC 200 mg/TDF 300 mg.

### 1.5.2. Main study

#### Patient exposure

In GS-US-174-0121, a total of 280 subjects (141 in the TDF group and 139 in the FTC/TDF group) were randomized and treated. The percentage of subjects with 96 weeks of study drug exposure was similar in the TDF (94.3%) and FTC/TDF (92.1%) groups. A total of 133 subjects received 96 weeks of continuous treatment with TDF, and 128 subjects received 96 weeks of continuous treatment with FTC/TDF.

The mean (standard deviation [SD]) duration of exposure to randomized study drug was 721.5 (149.73) days in the TDF group and 719.1 (137.25) days in the FTC/TDF group.

**Table 26.** GS-US-174-0121: Exposure to Study Drug (Safety Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| Days on Study Drug | | | |
| N | 141 | 139 | 280 |
| Mean (SD) | 721.5 (149.73) | 719.1 (137.25) | 720.3 (143.41) |
| Median | 757.0 | 757.0 | 757.0 |
| Q1, Q3 | 756.0, 758.0 | 755.0, 758.0 | 756.0, 758.0 |
| Min, Max | 2.0, 843.0 | 2.0, 840.0 | 2.0, 843.0 |
| Cumulative Duration of Exposure | | | |
| Baseline [Study Day 1] | 141 (100.0%) | 139 (100.0%) | 280 (100.0%) |
| Week 4 [Study Days 2 - 42] | 141 (100.0%) | 139 (100.0%) | 280 (100.0%) |
| Week 8 [Study Days 43 - 70] | 139 ( 98.6%) | 137 ( 98.6%) | 276 ( 98.6%) |
| Week 12 [Study Days 71 - 98] | 138 ( 97.9%) | 137 ( 98.6%) | 275 ( 98.2%) |
| Week 16 [Study Days 99 - 140] | 137 ( 97.2%) | 136 ( 97.8%) | 273 ( 97.5%) |
| Week 24 [Study Days 141 - 196] | 136 ( 96.5%) | 136 ( 97.8%) | 272 ( 97.1%) |
| Week 32 [Study Days 197 - 252] | 135 ( 95.7%) | 134 ( 96.4%) | 269 ( 96.1%) |
| Week 40 [Study Days 253 - 308] | 134 ( 95.0%) | 134 ( 96.4%) | 268 ( 95.7%) |
| Week 48 [Study Days 309 - 378] | 134 ( 95.0%) | 134 ( 96.4%) | 268 ( 95.7%) |
| Week 60 [Study Days 379 - 462] | 134 ( 95.0%) | 132 ( 95.0%) | 266 ( 95.0%) |
| Week 72 [Study Days 463 - 546] | 134 ( 95.0%) | 132 ( 95.0%) | 266 ( 95.0%) |
| Week 84 [Study Days 547 - 630] | 133 ( 94.3%) | 131 ( 94.2%) | 264 ( 94.3%) |
| Week 96 [Study Days 631 - 714] | 133 ( 94.3%) | 128 ( 92.1%) | 261 ( 93.2%) |

Exposure calculated as last dose date minus first dose date plus 1.

Programming Details: ...\version5\prog\t-exp.sas v9.2 Output file: t-exp.out 11MAY2012:14:19

Source: Module 5.3.5.1, GS-US-174-0121 Week 96 CSR, Section 15.1, Table 1.7

#### Adverse events

An overview of treatment emergent adverse events in study GS-US-174-0121 is provided in the table below.

**Table 27.** GS-US-174-0121: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| Number of Subjects who had any Treatment-Emergent AE | 99 ( 70.2%) | 98 ( 70.5%) | 197 ( 70.4%) |
| Number of Subjects who had any Grade 3 or 4 Treatment-Emergent AE | 4 ( 2.8%) | 15 ( 10.8%) | 19 ( 6.8%) |
| Number of Subjects who had any Grade 2, 3 or 4 Treatment-Emergent AE | 49 ( 34.8%) | 57 ( 41.0%) | 106 ( 37.9%) |
| Number of Subjects who had any Treatment-Emergent Treatment-Related AE | 26 ( 18.4%) | 29 ( 20.9%) | 55 ( 19.6%) |
| Number of Subjects who had any Grade 3 or 4 Treatment-Emergent Treatment-Related AE | 0 | 1 ( 0.7%) | 1 ( 0.4%) |
| Number of Subjects who had any Grade 2, 3 or 4 Treatment-Emergent Treatment-Related AE | 4 ( 2.8%) | 12 ( 8.6%) | 16 ( 5.7%) |
| Number of Subjects who had any Treatment-Emergent SAE | 8 ( 5.7%) | 17 ( 12.2%) | 25 ( 8.9%) |
| Number of Subjects who had any Treatment-Emergent Treatment-Related SAE | 0 | 1 ( 0.7%) | 1 ( 0.4%) |
| Number of Subjects who had any Treatment-Emergent AEs that caused Permanent Discontinuation from Study Drug | 1 ( 0.7%) | 2 ( 1.4%) | 3 ( 1.1%) |
| Number of Subjects who Died during Study | 1 ( 0.7%) | 2 ( 1.4%)[a] | 3 ( 1.1%)[a] |

Subjects were counted once only for each category by the most severe event.

a One additional subject (Subject 4018 in the FTC/TDF group) had a treatment-emergent SAE of bronchopneumonia that led to study discontinuation (see Section 11.5).

**Common Adverse Events**

The incidence of treatment-emergent AEs was similar between the TDF group (70.2%) and the FTC/TDF group (70.5%). The most frequently reported treatment-emergent AEs included headache (14.2% in the TDF group and 11.5% in the FTC/TDF group), nasopharyngitis (10.6% in the TDF group and 10.1% in the FTC/TDF group), and fatigue (7.1% in the TDF group and 10.8% in the FTC/TDF group). There were no statistically significant differences in the incidence of treatment-emergent AEs between the 2 treatment groups.

Grade 3 or 4 treatment-emergent AEs were reported by a higher percentage of subjects in the FTC/TDF group (10.8%) compared with the TDF group (2.8%). The only Grade 3 or 4 treatment-emergent AEs reported in 2 or more subjects were ALT increased (1 subject in the TDF group and 2 subjects in the FTC/TDF group), headache (1 subject in the TDF group and 1 subject in the FTC/TDF group), and depression (2 subjects in the FTC/TDF group).

The percentage of subjects who reported a treatment-emergent AE that was considered by the investigator to be related to study drug was similar between the 2 treatment groups (18.4% in the TDF group and 20.9% in the FTC/TDF group). The most frequently reported study drug-related AEs included fatigue (3.5% in the TDF group and 5.0% in the FTC/TDF group), nausea (2.8% in the TDF group and 4.3% in the FTC/TDF group), and headache (0.7% in the TDF group and 3.6% in the FTC/TDF group). Most study drug-related AEs were Grade 1 in severity, and most did not require dose

modification or interruption or discontinuation of study drug. The only Grade 3 or 4 study drug-related AE was flank pain in 1 subject in the FTC/TDF group.

**Adverse Events by Severity**

Grade 3 and 4 treatment-emergent AEs were reported in 2.8% of subjects (4 of 141) in the TDF group and 10.8% of subjects (15 of 139) in the FTC/TDF group. The only Grade 3 or 4 treatment-emergent AEs reported in 2 or more subjects were ALT increased (1 subject in the TDF group and 2 subjects in the FTC/TDF group), headache (1 subject in the TDF group and 1 subject in the FTC/TDF group), and depression (2 subjects in the FTC/TDF group).

**Treatment related AE**

**Table 28.** GS-US-174-0121: Treatment-Emergent Study Drug-Related Adverse Events Reported in 2 or More Subjects (Safety Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| Number Of Subjects With Any Event | 26 ( 18.4%) | 29 ( 20.9%) | 55 ( 19.6%) |
| GASTROINTESTINAL DISORDERS | 12 ( 8.5%) | 12 ( 8.6%) | 24 ( 8.6%) |
| DIARRHOEA | 3 ( 2.1%) | 1 ( 0.7%) | 4 ( 1.4%) |
| DYSPEPSIA | 1 ( 0.7%) | 2 ( 1.4%) | 3 ( 1.1%) |
| ABDOMINAL DISTENSION | 2 ( 1.4%) | 0 | 2 ( 0.7%) |
| FLATULENCE | 2 ( 1.4%) | 0 | 2 ( 0.7%) |
| ABDOMINAL PAIN UPPER | 0 | 3 ( 2.2%) | 3 ( 1.1%) |
| ABDOMINAL DISCOMFORT | 1 ( 0.7%) | 2 ( 1.4%) | 3 ( 1.1%) |
| NAUSEA | 4 ( 2.8%) | 6 ( 4.3%) | 10 ( 3.6%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 5 ( 3.5%) | 7 ( 5.0%) | 12 ( 4.3%) |
| FATIGUE | 5 ( 3.5%) | 7 ( 5.0%) | 12 ( 4.3%) |
| INVESTIGATIONS | 4 ( 2.8%) | 10 ( 7.2%) | 14 ( 5.0%) |
| ALANINE AMINOTRANSFERASE INCREASED | 1 ( 0.7%) | 2 ( 1.4%) | 3 ( 1.1%) |
| CREATININE RENAL CLEARANCE DECREASED | 0 | 5 ( 3.6%) | 5 ( 1.8%) |
| METABOLISM AND NUTRITION DISORDERS | 1 ( 0.7%) | 3 ( 2.2%) | 4 ( 1.4%) |
| DECREASED APPETITE | 0 | 2 ( 1.4%) | 2 ( 0.7%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 6 ( 4.3%) | 9 ( 6.5%) | 15 ( 5.4%) |
| ARTHRALGIA | 1 ( 0.7%) | 3 ( 2.2%) | 4 ( 1.4%) |
| MYALGIA | 1 ( 0.7%) | 1 ( 0.7%) | 2 ( 0.7%) |
| BACK PAIN | 0 | 4 ( 2.9%) | 4 ( 1.4%) |
| NERVOUS SYSTEM DISORDERS | 3 ( 2.1%) | 7 ( 5.0%) | 10 ( 3.6%) |
| HEADACHE | 1 ( 0.7%) | 5 ( 3.6%) | 6 ( 2.1%) |
| DIZZINESS | 0 | 4 ( 2.9%) | 4 ( 1.4%) |
| PSYCHIATRIC DISORDERS | 2 ( 1.4%) | 0 | 2 ( 0.7%) |
| INSOMNIA | 2 ( 1.4%) | 0 | 2 ( 0.7%) |
| RENAL AND URINARY DISORDERS | 3 ( 2.1%) | 4 ( 2.9%) | 7 ( 2.5%) |
| PROTEINURIA | 1 ( 0.7%) | 2 ( 1.4%) | 3 ( 1.1%) |
| HAEMATURIA | 2 ( 1.4%) | 0 | 2 ( 0.7%) |

Events coded using MedDRA dictionary 14.1. Subjects were counted once only for each category.

Programming Details: ...\version5\prog\t-ae.sas v9.2 Output file: t-aerel.out 11MAY2012:14:12

Source: Section 15.1, Table 3.5; Appendix 16.2, Listing 3.1

In general drug-related AEs were more frequent in the FTC/TDF group (20.9% versus 18.4% in TDF-treated patients). Gastrointestinal disorders were the most commonly AEs reported by SOC. Fatigue (3.5% and 5.0% in the TDF and FTC/TDF groups respectively), nausea (2.8% and 4.3% in the TDF and the FTC/TDF group) and headache (0.7% and 3.6%) were the more frequently reported treatment related AEs. Similarly, more patients experienced treatment-related AEs of Grade 2 or higher in the combination group (8.6% in the FTC/TDF group versus 2.8% in the TDF-treated patients). Fatigue and

headache were the only grade 2 (or higher) treatment-related AEs reported in more than 1 subject (fatigue in 4 subjects in the FTC/TDF group and headache in 2 subjects in the FTC/TDF group).

## Serious adverse event / deaths / other significant events

### Deaths

There were three deaths during study period. The causes of death included gastrointestinal hemorrhage, cardiac arrest, and bronchopneumonia; all considered unrelated to study drug. All of these deaths occurred prior to Week 96. In addition, 1 subject died due to an SAE of hepatocellular carcinoma before starting study medication (ie, pre-randomization).

### Serious adverse events

Treatment-emergent SAEs were reported in 5.7% of subjects (8 of 141) in the TDF group and 12.2% of subjects (17 of 139) in the FTC/TDF group. Treatment-emergent SAEs reported in 2 or more subjects included ALT increased in 4 subjects (1 in the TDF group and 3 in the FTC/TDF group), gastritis in 2 subjects (1 in the TDF group and 1 in the FTC/TDF group), and osteoarthritis in 2 subjects (both in the FTC/TDF group).

### Adverse events of special interest

- **Renal disorders**

*Renal Adverse events*

Treatment-emergent AEs in the renal and urinary disorders system organ class were reported in 2.8% of subjects (4 of 141) in the TDF group and 7.2% of subjects (10 of 139) in the FTC/TDF group. The most frequently reported treatment-emergent renal and urinary disorder AEs included proteinuria in 4 subjects (1 in the TDF group and 3 in the FTC/TDF group), mild nephropathy in 3 subjects (1 in the TDF group [unrelated to study drug] and 2 in the FTC/TDF group [1 study drug related, 1 unrelated to study drug]), hematuria in 3 subjects (all in the TDF group), and glycosuria in 2 subjects (both in the FTC/TDF group). All other renal and urinary disorder AEs were reported in 1 subject each and included tubulo-interstitial nephritis in the TDF group and nephrolithiasis, nocturia, and renal colic in the FTC/TDF group. None resulted in permanent discontinuation of study drug.

*Renal laboratory abnormalities*

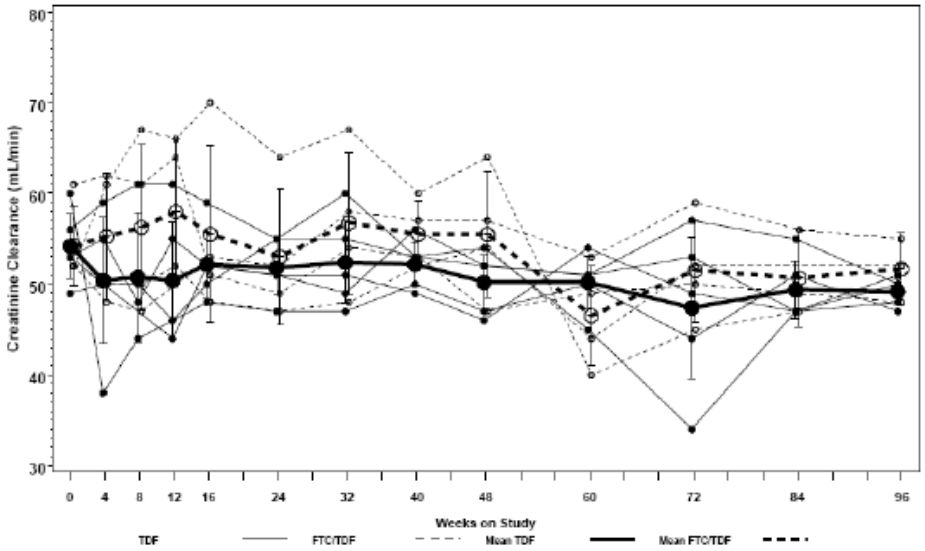
A total of 28 subjects (14 in the TDF group and 14 in the FTC/TDF group) had at least one marked clinical laboratory abnormality. The incidence of each individual marked laboratory abnormality was low (<4% of subjects in either treatment group).

No subject had a confirmed increase from baseline in serum creatinine of at least 0.5 mg/dL. Two subjects (both in the TDF group) had a confirmed serum phosphorus concentration of <2 mg/dL. A total of 9 subjects (5 in the TDF group and 4 in the FTC/TDF group) had a confirmed CLcr rate of < 50 mL/min. All 9 of these subjects had a baseline Clcr rate between 49−61 mL/min (by Cockcroft-Gault calculation). By Week 96, 4 of these subjects had Clcr < 50 mL/min, 4 subjects had Clcr ≥50 mL/min, and 1 subject had a last Clcr value of 47 mL/min (confirmed) at Week 84 (subject discontinued from the study prematurely due to an SAE of pneumonia).

**Table 29.** GS-US-174-0121: Confirmed Renal Abnormalities (Safety Analysis Set)

| | TDF (N=141) | FTC/TDF (N=139) | Total (N=280) |
|---|---|---|---|
| Number of Subjects Who Had Confirmed Increase in Creatinine of at Least 0.5 mg/dL | 0 | 0 | 0 |
| Number of Subjects Who Had Confirmed Creatinine Clearance Below 50 mL/min (Calculated using Cockcroft-Gault) | 5 ( 3.5%) | 4 ( 2.9%) | 9 ( 3.2%) |
| Number of Subjects Who Had Confirmed Phosphorus Below 2 mg/dL | 2 ( 1.4%) | 0 | 2 ( 0.7%) |
| Number of Subjects Who Had Confirmed Increase in Creatinine of at Least 0.5 mg/dL and Confirmed Phosphorus Below 2 mg/dL | 0 | 0 | 0 |

**Figure 5.** Creatinine Clearance (Cockcroft-Gault) by Visit for Subjects with Confirmed Creatinine Clearance (Cockcroft-Gault) < 50 mL/min




As illustrated in the graph above, renal function of patients who experienced CrCl <50ml/min seems to remain stable during the study. No patients discontinued for renal disorders at Week 96. Longer term data are awaited to further assess renal tolerance of TDF in patients with mild renal impairment at baseline.

- **Hepatobiliary disorders**

*Hepatobiliary AE*

Treatment-emergent AEs in the hepatobiliary disorders system organ class were reported in 0.7% of subjects (1 of 141) in the TDF group and 2.2% of subjects (3 of 139) in the FTC/TDF group. All treatment-emergent hepatobiliary disorder AEs were reported in 1 subject each and included hepatic pain in the TDF group and cholelithiasis, hepatic cirrhosis, and hepatomegaly in the FTC/TDF group. No hepatobiliary AEs were considered related to study drug, and none resulted in dose modification or interruption or discontinuation of study drug.

*Hepatic flare:*

- On-treatment: On-treatment hepatic flares (>2 X baseline value and >10 X ULN) were reported in 3 subjects (2 subjects in the TDF group and 1 subject in the FTC/TDF group). The hepatic flares

for each of these subjects resolved, and study drug was continued. The hepatic flares were accompanied by continued decreases in HBV DNA.

- Off-treatment: One subject in the FTC/TDF group experienced an off-treatment hepatic flare after discontinuing study drug due to pregnancy (see below). Approximately 2 months after discontinuing study drug, the subject had a severe SAE of ALT increased (an off-treatment ALT flare) on Day 251 (Grade 4 ALT peak value was 2285 U/L on Day 251, which was >2 X baseline and >10 X ULN and was accompanied by Grade 1 decrease in albumin and normal total bilirubin [0.5 mg/dL]). The SAE of ALT increased was resolved by Day 308 and was considered to be unrelated to study drug. Pregnancy outcome information was provided to DSPH after the data cut-off for this interim Week 96 analysis. At 40 weeks of gestational age, the subject gave birth to a healthy female infant.

- **Bone disorders**

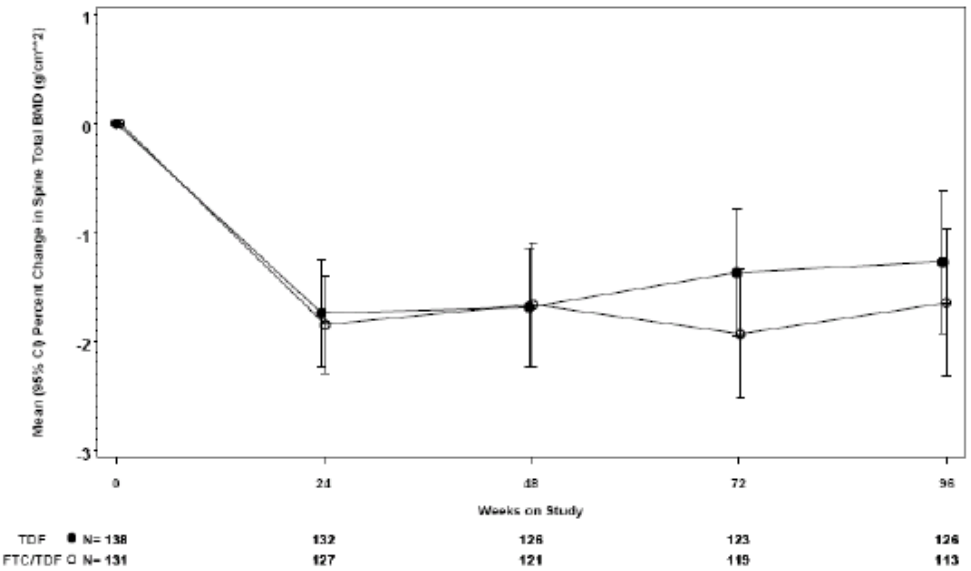
*Bone-related AE*

Treatment-emergent fractures were reported in 5 subjects (3 in the TDF group and 2 in the FTC/TDF group). None of the fractures were considered related to study drug, and none resulted in dose modification or interruption or discontinuation of study drug. All fractures were noted as trauma related.

*Bone DEXA measurement:*

- Spine: Lumbar spine total BMD (g/cm2) initially decreased from baseline to Week 24 in both treatment groups, and subsequently plateaued with minimal further decreases in BMD observed from Weeks 24 to 96. The mean (SD) percentage decrease in spine total BMD from baseline to Week 24 was −1.74% (2.87%) in the TDF group (n = 132) and −1.85% (2.57%) in the FTC/TDF group (n = 127). The mean (SD) percentage decrease in spine total BMD from baseline to Week 96 was −1.27% (3.78%) in the TDF group (n = 126) and −1.65% (3.68%) in the FTC/TDF group (n = 113).

**Figure 6.** GS-US-174-0121: Mean Percent Change from Baseline in Total Spine Bone Mineral Density (g/cm$^2$) by Visit (Safety Analysis Set)

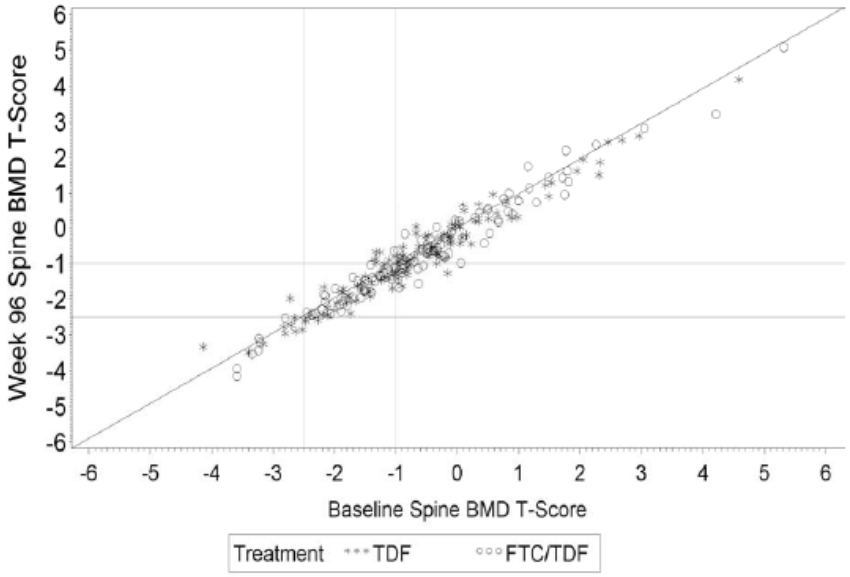



A similar pattern of change in spine BMD was apparent in spine BMD T-scores and Z-scores over the first 96 weeks of the study (ie, scores were decreased by Week 24, and then remained relatively stable over Weeks 24 to 96). The mean (SD) decrease in spine BMD T-scores from baseline to Week 24 was −0.17 (0.257) in the TDF group (n = 132) and −0.17 (0.233) in the FTC/TDF group (n = 127). The

mean (SD) decrease in spine BMD Z-scores from baseline to Week 24 was −0.16 (0.259) in the TDF group (n = 132) and −0.16 (0.234) in the FTC/TDF group (n = 127). After Week 24, minimal changes were observed in spine T-scores and Z-scores through Week 96. There were no statistically significant differences in spine total BMD, T-score, or Z-score changes from baseline between the TDF and FTC/TDF groups at any post-dose time point.

At baseline, 60% of subjects (83 of 138) in the TDF group and 58% of subjects (76 of 131) in the FTC/TDF group had normal spine BMD T-scores (≥−1). Baseline T-scores for spine BMD were −1 to −2.5 (consistent with osteopenia) in 32% of subjects (44 of 138) in the TDF group and 36% of subjects (47 of 131) in the FTC/TDF group. Baseline T-scores for spine BMD were < −2.5 (consistent with osteoporosis) in 8% of subjects (11 of 138) in the TDF group and 6% of subjects (8 of 131) in the FTC/TDF group. From baseline to Week 96, the clinical status category (ie, ≥−1 [normal], −1 to −2.5 [consistent with osteopenia], or < −2.5 [consistent with osteoporosis]) for spine BMD T-score improved for 7 subjects and worsened for 22 subjects in the overall population (n = 269, p = 0.051). In the overall population, 3 subjects shifted from a spine T-score consistent with osteopenia at baseline to a spine T-score consistent with osteoporosis at Week 96, and 1 subject shifted from a spine T-score consistent with osteoporosis at baseline to a spine T-score consistent with osteopenia at Week 96.

**Figure 7.** GS-US-174-0121: Week 96 Spine T-score Versus Baseline Spine T-Score (Safety Analysis Set)



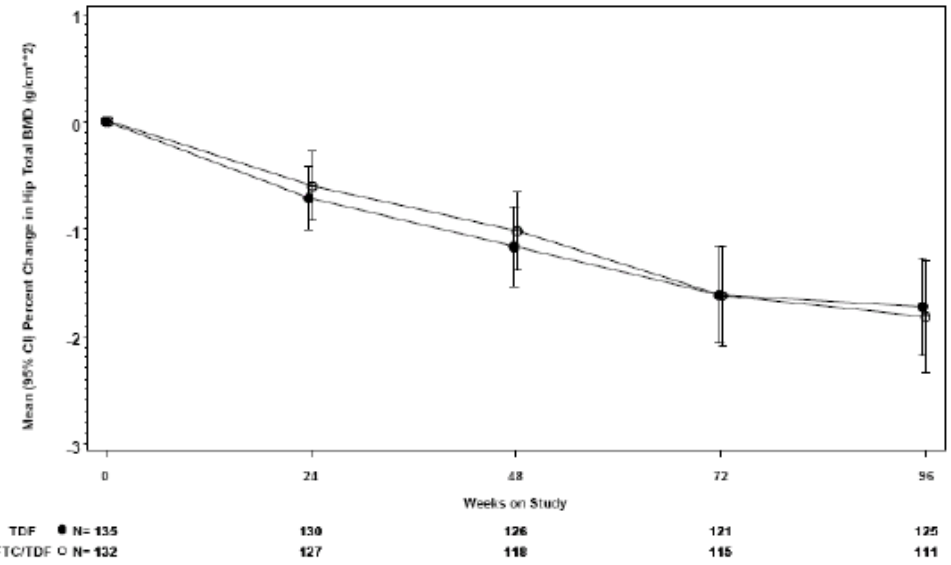

At baseline, 91% of subjects (126 of 138) in the TDF group and 91% of subjects (119 of 131) in the FTC/TDF group had normal spine BMD Z-scores (≥−2). Baseline Z-scores for spine BMD were below the expected range for age (< −2) in 9% of subjects (12 of 138) in the TDF group and 9% of subjects (12 of 131) in the FTC/TDF group. From baseline to Week 96, the clinical status category for spine BMD Z-score in the overall population improved (ie, shifted from a spine Z-score < −2 to a spine Z-score ≥−2) for 3 subjects and worsened (ie, shifted from a spine Z-score ≥−2 to a spine Z-score < −2) for 3 subjects (n = 269).

- Hip: Compared to changes observed in spine BMD, decreases in hip BMD occurred more gradually throughout the first 96 weeks of the study, reaching the lowest point at Week 96.

The mean (SD) percentage decrease in hip total BMD from baseline to Week 96 was −1.73% (2.593%) in the TDF group (n = 125) and −1.82% (2.825%) in the FTC/TDF group (n = 111).

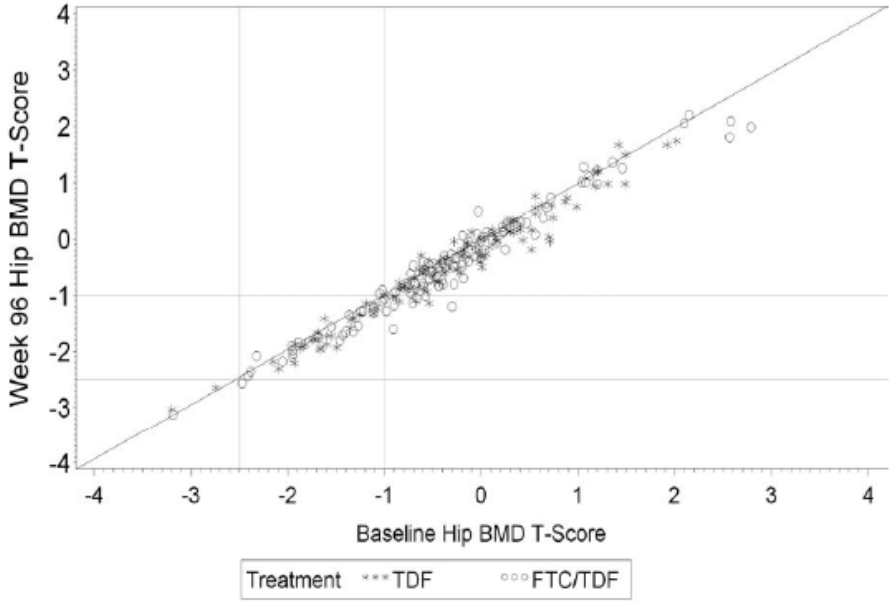
Similar gradual decreases in hip BMD T-scores and Z-scores were apparent over the first 96 weeks of the study. The mean (SD) decrease in hip BMD T-scores from baseline to Week 96 was −0.13 (0.194) in the TDF group (n = 125) and −0.14 (0.221) in the FTC/TDF group (n = 111). The mean (SD) decrease in hip BMD Z-scores from baseline to Week 96 was −0.09 (0.191) in the TDF group (n = 125) and −0.10 (0.219) in the FTC/TDF group (n = 111). There were no statistically significant differences in hip total BMD, T-score, or Z-score changes from baseline between the TDF and FTC/TDF groups at any post-dose time point.

**Figure 8.** GS-US-174-0121: Mean Percent Change from Baseline in Hip Total Bone Mineral Density ($g/cm^2$) by Visit (Safety Analysis Set).




At baseline, 79% of subjects (107 of 135) in the TDF group and 74% of subjects (98 of 132) in the FTC/TDF group had normal hip BMD T-scores (≥−1). Baseline T-scores for hip BMD were −1 to −2.5 (consistent with osteopenia) in 19% of subjects (26 of 135) in the TDF group and 25% of subjects (33 of 132) in the FTC/TDF group. Baseline T-scores for hip BMD were < −2.5 (consistent with osteoporosis) in 1% of subjects (2 of 135) in the TDF group and 1% of subjects (1 of 132) in the FTC/TDF group. From baseline to Week 96, the clinical status category for hip BMD T-score in the overall population improved for 2 subjects and worsened for 14 subjects (n = 267, p = 0.028). In the overall population, only 1 subject shifted from a hip T-score consistent with osteopenia at baseline to a hip T-score consistent with osteoporosis at Week 96, and no subject shifted from a hip T-score consistent with osteoporosis at baseline to a hip T-score consistent with osteopenia at Week 96.

**Figure 9.** GS-US-174-0121: Week 96 Hip BMD T-score Versus Baseline Hip BMD T-score (Safety Analysis Set).




At baseline, 99% of subjects (134 of 135) in the TDF group and 97% of subjects (128 of 132) in the FTC/TDF group had normal hip BMD Z-scores (≥−2). Baseline Z-scores for hip BMD were below the expected range for age (< −2) in 1% if subjects (1 of 135) in the TDF group and 3% of subjects (4 of 132) in the FTC/TDF group. From baseline to Week 96, the clinical status category for hip BMD Z-score in the overall population improved (ie, shifted from a hip Z-score < −2 to a hip score ≥−2) for 1 subject and worsened (ie, shifted from a hip Z-score ≥−2 to a hip Z-score < −2) for 2 subjects (n = 267).

## Laboratory findings

The most frequently reported treatment-emergent marked laboratory abnormalities included urine blood (5 subjects in the TDF group and 3 subjects in the FTC/TDF group), urine glucose (1 subject in the TDF group and 3 subjects in the FTC/TDF group), prolonged prothrombin time (2 subjects in the TDF group and 2 subjects in the FTC/TDF group), elevated ALT (2 subjects in the TDF group and 2 subjects in the FTC/TDF group), increased serum amylase (2 subjects in the FTC/TDF group), decreased phosphorus (1 subject in the TDF group and 1 subject in the FTC/TDF group), decreased platelets (1 subject in the TDF group and 1 subject in the FTC/TDF group), and elevated AST

The most commonly (> 2 subjects) reported Grade 3 or 4 treatment-emergent laboratory abnormalities included urine blood (11 subjects), urine glucose (10 subjects), increased ALT (10 subjects), increased AST (7 subjects), elevated fasting serum glucose (5 subjects), increased serum amylase (4 subjects), prolonged prothrombin time (4 subjects), and increased uric acid (3 subjects).

Of the 11 subjects with treatment-emergent Grade 3 or 4 blood in the urine, all except 1 subject were female, suggesting that menstrual contamination may have contributed to these findings.

Of the 10 subjects with treatment-emergent Grade 3 or 4 urine glucose, all except 2 subjects (Subjects 4196-1018 and 4848-4070 in the FTC/TDF group) had a medical history of diabetes mellitus. Of the 5 subjects with treatment-emergent Grade 3 or 4 increases in fasting serum glucose, 2 were in the TDF group and 3 were in the FTC/TDF group. All 5 subjects had a medical history of diabetes mellitus.

## Discontinuation due to adverse events

Four subjects permanently discontinued study drug due to a treatment-emergent AE (1 in the TDF group and 3 in the FTC/TDF group). All treatment-emergent AEs resulting in discontinuation of study drug were reported in 1 subject each and included neutropenia, malignant lung neoplasm, bronchopneumonia, and fatigue/bone pain/headache/somnolence/hypoesthesia. The AEs of fatigue, bone pain, headache, and somnolence were considered to be related to study drug; the other AEs leading to discontinuation were considered unrelated.

## Ancillary analyses

Cirrhotic patients

In the 9 subjects with known cirrhosis participating in Study 121, study drug treatment was generally safe and well tolerated.

None of the subjects in this subset discontinued treatment for an AE related to study drug, and none experienced a Grade 3 or 4 drug-related AE or a Grade 3 or 4 laboratory abnormality reported as an AE.

There were only 2 subjects, both in the FTC/TDF group, (Nos. 4037-1013 and 1591-4056) who experienced SAEs during the study, none of which were considered related to study drug.

Subject 4037-1013, a 58-year-old white male with a history of diabetes mellitus and hypertension, was diagnosed with HCC during the study. This subject died from cardiac arrest on Day 711 related to SAEs of sepsis, abdominal infection, and diarrhea.

Subject 1591-4056 experienced an SAE of HCC (moderate) on Day 421 (no date of resolution provided). Earlier in the study, this subject had experienced 2 separate episodes of creatinine clearance (CLcr) decreased (mild) on Days 225 (CLcr was 71 mL/min; Cockcroft-Gault calculation) through 281 (CLcr was 78 mL/min; Cockcroft-Gault calculation) and again on Day 337 (CLcr was 68 mL/min; Cockcroft-Gault calculation) (no date of resolution provided; last available value was 67 mL/min on Day 679, Week 96;Cockcroft-Gault calculation). Both of these AEs of CLcr decreased were considered by the investigator to be study drug related.

Other reported adverse events (AEs) of clinical relevance (renal and bone related) in this subgroup were as follows. Three of these subjects reported AEs that were considered by the investigator to be study drug related: Subject 4530-4102 (TDF group) experienced an AE on Day 167 of osteoporosis (no date of resolution provided); Subject 1591-4017 (FTC/TDF group) experienced an AE of creatinine renal clearance decreased on Day 421 (no date of resolution provided); and Subject 1591-4069 (FTC/TDF group) reported an AE of creatinine clearance decreased on Day 337 (no date of resolution provided). All of these treatment-related AEs were mild in severity.

Comparison of key safety results in patients with CrCl < 80 versus > 80 ml/min

The MAH conducted an ad hoc analyses of key safety results (AEs, renal-laboratory assessments, and BMD) in renally impaired subjects (n= 74 patients with mild renal impairment) compared with subjects with normal renal function (n=206).

Subjects with baseline CLcr > 80 mL/min were significantly younger (median age 42.0 years) than those with baseline CLcr < 80 mL/min, more were male (81.1%) and they had significantly greater median ALT and fewer prior IFN or ADV exposure.

***Treatment-emergent AE:***

The proportions of subjects experiencing AEs were slightly higher in the lower CLcr category (77%) versus the higher baseline CLcr category (68.0%); however, this difference was not statistically significant and was driven by the fact that more subjects in the lower baseline CLcr category experienced metabolism and nutritional disorders (12.2%) than those in the higher baseline CLcr category (2.4%) (p = 0.015).

As expected, more subjects in the lower CLcr category experienced decreased creatinine clearance (6.8% versus 1.5% in the higher baseline CLcr category) (p = 0.032).

Adverse events leading to discontinuations were summarized by baseline CLcr category and by baseline CLcr category and treatment; there were no notable differences between CLcr categories in the frequency or nature of AEs leading to discontinuation

***Renal:***

Mean change from baseline to Week 96 in serum creatinine was small and identical in both baseline CLcr categories (0.07 mg/dL). Moreover, mean serum phosphorus decreased similarly from baseline to Week 96 in both the lower (-0.06 mg/dL) and higher (-0.03 mg/dL) baseline CLcr groups.

Mean baseline CLcr for subjects in the lower baseline CLcr category was 67.1 mL/min; in the higher CLcr category mean baseline CLcr was 103.6 mL/min. Mean CLcr decreased from baseline to Week 96 in both the lower and higher CLcr groups, but more so in the higher baseline CLcr group (−9.1 mL/min) than the lower CLcr group (−5.5 mL/min).

Of note, 9 of 74 subjects (12.2%) in the lower baseline CLcr category experienced confirmed creatinine clearance below 50 mL/min, and 2 of 206 subjects (1.0%) in the higher baseline CLcr category experienced confirmed serum phosphorus below 2 mg/dL.

***Bone:***

Baseline mean (SD) total spine BMD was similar between the lower (1.05 [0.215] g/cm2) and higher (1.07 [0.177] g/cm2) CLcr categories, and mean (SD) change from baseline to Week 96 was also similar between baseline CLcr categories (−1.68 [3.602] g/cm2 lower CLcr category, −1.37 [3.777] g/cm2 higher CLcr category) (p = 0.46). Mean (SD) change from baseline to Week 96 in total spine BMD T-score and Z-score were similar between baseline CLcr categories.

Baseline mean (SD) total hip BMD was similar between the lower (0.96 [0.181] g/cm2) and higher (1.00 [0.141] g/cm2) CLcr categories, and mean (SD) change from baseline to Week 96 was also similar between baseline CLcr categories (−2.30 [2.702] g/cm2 lower CLcr category, −1.58 [2.681] g/cm2 higher CLcr category) (p = 0.13). Mean (SD) change from baseline to Week 96 in total hip BMD T-score and Z-score were similar between baseline CLcr categories.

## Post marketing experience

Viread was first approved in the US on 26 October 2001 and has an International Birth Date of 31 October 2001.

The cumulative worldwide patient exposure to TDF (alone and in combination products Truvada, Atripla, and Eviplera/Complera) from first marketing approval in the US on 26 October 2001 to 31 March 2012 is estimated to be over 5 million patient-years of treatment.

No new safety signals have been identified in the assessment of safety data for TDF in patients with CHB in the Gilead DSPH database.

## 1.5.3. Discussion on clinical safety

The safety analysis set from ongoing study GS-US-174-0121 includes 141 subjects who received TDF 300 mg and 139 subjects who received FTC 200 mg/TDF 300 mg. The mean duration of treatment for TDF-exposed patients was similar between treatment groups: 721.5 days in the TDF group and 719.1 days in the FTC/TDF group. In addition, long-term data in CHB are currently available from the open-label extension phase of studies 102&103 consisting of treatment with TDF up to 384 weeks (year 8).

For the clinical trial GS-US-174-0121, the frequency of AEs was similar for both treatment groups (70.2% for the TDF group and 70.5% for the FTC/TDF population) as well as the proportion of subjects reporting one treatment-related AE (18.4% in the TDF group versus 20.9% in the FTC/TDF group). However, higher frequency of grade 2, 3 or 4 treatment-related AE was reported in FTC/TDF-treated patients (8.6%) compared to TDF-treated patients (2.8%).

No new adverse events have been identified. As expected, the SOC more frequently reported was “Gastrointestinal disorders”. Fatigue (3.5% and 5.0% in the TDF and FTC/TDF groups respectively), nausea (2.8% and 4.3% in the TDF and the FTC/TDF group) and headache (0.7% and 3.6%) were the more commonly reported treatment-related AEs. Similarly, more patients experienced treatment-related AEs of Grade 2 or higher in the combination group (8.6% in the FTC/TDF group versus 2.8% in the TDF-treated patients).

Special attention was paid to liver AEs, renal toxicity and bone toxicity. No new concerns were raised. Few patients reported hepatic AEs (0.7% in TDF population and 2.2% in the FTC/TDF group). Only 3 patients (2 in the TDF group and 1 in the FTC/TDF population) experienced ALTs flares. In general, in line with previous findings, data do not suggest major liver toxicity. The current wording stated in SmPC section 4.4 on the risk of hepatitis exacerbations during TDF treatment is considered appropriate.

No major issues related to renal toxicity were identified. New concerns regarding the bone toxicity have not been observed either. An unexpected pattern of decrease in hip BMD was nevertheless observed, with gradual decrease not reaching a plateau at Week 96. Even though mean change from baseline in hip BMD remains small, this will need to be closely monitored in longer term reports and the potential for bone toxicity should continue to be monitored in future PSURs.

A higher proportion of subjects experienced treatment-emergent SAEs in the FTC/TDF group (12.2%) compared to the TDF group (5.7%). Three deaths occurred during study period. None of them were considered related to the study drug.

## 1.5.4. Conclusions on clinical safety

In conclusion, no new AEs have been identified in this lamivudine-resistant population. The safety profile of TDF in patients with LAM-R in this study was consistent with the known safety profile of TDF as previously described in patients with CHB. In particular no major liver, renal or bone toxicities were reported in this study. An unexpectedly pattern of decrease in hip BMD was nevertheless observed, with gradual decrease not reaching a plateau at Week 96. Even though mean change from baseline in hip BMD remains small (as was also observed for hip BMD), this will need to be closely monitored in longer term reports and the potential for bone toxicity should continue to be monitored in future PSURs.

Moreover, this study was identified as part of FUM 234 [Submission of a comprehensive plan to generate data regarding the safety, exposure, and tolerability of Viread in patients with creatinine clearance 20 to 60 ml/min] as a source of information as regards the safety of Viread in patients with impaired renal function. In this study patients with CrCl 50-80 ml/min could have been included (whereas more stringent criterion is generally applied) and a total of 74 patients (41 in the TDF arm and 33 in the TDF/FTC arm) had 50ml/min>CrCl<80 ml/min at baseline. Comparison of the safety profile between patients with baseline CrCl <80 ml/min versus those with baseline CrCl $\geq$80 ml/min did not indicate significant difference in the safety profile (and notably no obvious deterioration of the renal function) in patients with mild renal impairment compared to those with normal renal function in this study

### 1.5.5. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 31 March 2013.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

## *1.6. Risk management plan*

### 1.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

**PRAC Advice**

Based on the PRAC review of the Risk Management Plan version 12.3 of 24 August 2012, the PRAC considers by consensus that the risk management system for Tenofovir Disoproxil Fumarate (Viread) in the treatment of proposed indication is acceptable. The following points should be taken into account in the next routine update of the RMP:

1. Epidemiology of resistance to lamivudine in patients with chronic hepatitis B should be provided.
2. Relevant non clinical data regarding TDF related bone toxicity should be provided when the RMP will be format to the new template
3. Clinical exposure in patients with chronic hepatitis B (CHB) who are resistant to lamivudine (LAM-R) should be provided
4. As regards the section detailing important identified risk (section 2.3.4.2.1), the renal toxicity section has not been updated to incorporate newly available data from study GS-US-174-0121 and week 288 analyses of studies GS-US-174-0102 and GS-US-174-0103. However, renal data from these studies were reflected in other parts of the RMP. For the sake of completeness, there might be a need to update this section as well; this should be commented by the MAH.
5. The applicant should discuss the points raised in assessment report of RMP 12.0:
    1) In vitro studies on human colonic cell line caco-2 to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the gastrointestinal (GI) tract have been completed and removed from this updated RMP. Due to the lack of consistency in the behavior of phosphate in the assay, phosphate uptake in a caco-2 monolayer cell assay does not appear to be a useful approach. No additional nonclinical studies are planned. However, the MAH should discuss the usefulness of other in vitro, as well as

in vivo, approaches for assessing the potential inhibitory effect of tenofovir DF on absorption of phosphate in the gastrointestinal tract.

2) Given the small sample size in studies GS-US-174-0108 and GS-US-174-0107, especially regarding patients with CPT score >9 (8 subjects with a baseline CPT score >9 in study -108 and 34 subjects with Orthotopic Liver Transplant who completed 96 weeks of study -107), safety in patients with decompensated liver diseases and CPT score>9 (including long term safety) and safety in liver transplant recipients should continue to be monitored and separately reported in the PSUR. Therefore, in order to keep coherence between the RMP and the PSUR, these concerns should be maintained as " missing information" in the RMP.

3) The current educational materials have been endorsed in April 2011. Meanwhile, the HIV physician survey was made available that yield interesting results that may improve the renal risk minimisation activities. Therefore, the MAH is requested to discuss the following comments:

   - The MAH should consider improvements to the brochure section regarding renal function monitoring, eg:
     - As for dosing interval adjustment, a tabular presentation of recommended renal monitoring schedule might deliver more efficient information and should be considered.
     - Monthly monitoring of serum phosphate should be highlighted
     - Monthly renal function monitoring should be mentioned separately, for the initiation period (0-6 month) and the 6-12 month treatment period.
   - The MAH should consider adding the following information in the renal brochure:
     - some severe renal AEs have been reported
     - reversibility of TDF renal toxicity has not been established
     - the time to onset of the renal ADRs for subjects receiving TDF had a broad range (In clinical studies, time to onset from 29 to 1291 days, with a median of 296 days (~ 9 months) and in spontaneous reporting (latest PSUR Section 9.1.1.2), 50% of the cases occur within the first year, including 17% during the 6-12 month treatment period)

4) The results of the survey of HBV physicians are similar to those observed for HIV physicians and raise the same comments.

5) For the following updated versions of RMP, the MAH is requested to also submit tracked change versions

This advice is based on the following content of the Risk Management Plan:

***Safety concerns***

The MAH identified the following safety concerns in the RMP:

**Table 30.** Summary of the Safety Concerns

| | |
|---|---|
| Important Identified Risks | Renal toxicity |
| | Bone events due to proximal renal tubulopathy/loss of bone mineral density |
| | Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients |
| | Interaction with didanosine |
| | Pancreatitis |
| | Lactic acidosis and severe hepatomegaly with steatosis |
| | Lipodystrophy |
| Important Potential Risks | Development of resistance during long-term exposure in HBV infected patients |
| Missing Information | Safety in children (including long-term safety) |
| | Safety in elderly patients |
| | Safety in pregnancy |
| | Safety in lactation |
| | Safety in black HBV infected patients |
| | Safety in patients with renal impairment |

The PRAC considers that the following issues should be addressed:

- safety in patients with decompensated liver diseases and CPT score>9 (including long term safety) and safety in liver transplant recipients should be maintained as " missing information".

***Pharmacovigilance plans***

**Table 31.** Ongoing and planned studies in the PhV development plan

| **Study / activity** Type, title and category (1-3) | **Objectives** | **Safety concerns addressed** | **Status** (planned, started) | **Date for submission of interim or final reports** (planned or actual) |
|---|---|---|---|---|
| ***Clinical Studies*** | | | | |
| GS-99-903 | A Phase III, randomized, double-blind, multicenter study of the treatment of antiretroviral-naive, HIV-1 infected patients comparing tenofovir disoproxil fumarate administered in combination with lamivudine and efavirenz versus stavudine, amivudine, and efavirenz. | bone mineral density | Ongoing | Final report anticipated 31 March 2014 |
| GS-US-236-0103 | A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy Of Elvitegravir/Emtricitabine/ Tenofovir Disoproxil Fumarate/GS- 9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults | bone mineral density | Ongoing | Week 96 report anticipated Q2 2013 |
| GS-US-104-0321 (adolescents) | A Phase III, Randomized, Double-Blind, Placebo Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen of HIVInfected Children and Adolescents | bone mineral density<br>Safety in children (including long-term safety) | Ongoing | Final Week 336 report anticipated December 2014 |
| GS-US-104-0352 (children) | A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in virologically Suppressed HIVInfected Children Taking Highly active Antiretroviral Therapy | bone mineral density<br>Safety in children (including long-term safety) | Ongoing | Final Week 336 report anticipated May 2015 |
| GS-US-174-0102 | A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of Presumed Pre-Core Mutant Chronic Hepatitis B | bone mineral density<br>Development of resistance during long-term exposure in HBV infected patients | Ongoing | Final report anticipated Q3 2014 |
| GS-US-174-0103 | A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of HBeAg Positive Chronic Hepatitis B | bone mineral density<br>Development of resistance during long-term exposure in HBV infected patients | Ongoing | Final report anticipated Q3 2014 |
| GS-US-174-0115 (adolescents) | A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection | bone mineral density<br>Safety in children (including long-term safety) | Ongoing | Final Week 192 report anticipated Q4 2013 |

| | | | | |
|---|---|---|---|---|
| GS-US-174-0121 | A Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects with Chronic Hepatitis B who are Resistant to Lamivudine | bone mineral density<br>Development of resistance during long-term exposure in HBV infected patients<br>Safety in patients with renal impairment | Ongoing | Final report anticipated Q2 2015 |
| GS-US-174-0127 | A Phase 2, Multi-center, Open-label Study of Tenofovir Disoproxil Fumarate (DF) for the Treatment of Chronic Hepatitis B Subjects with Compensated or Decompensated Liver Disease and Moderate to Severe Renal Impairment | Safety in patients with renal impairment | Planned | To be confirmed |
| GS-US-174-0144 (children) | A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infectio | bone mineral density<br>Safety in children (including long-term safety) | Planned | Week 24 report anticipated Q2 2015. PK Data anticipated to be submitted by Q2 2014 |
| PK bioavailability study of TDF oral granules | To evaluate the formulation performance of tenofovir DF oral granules with both a light and high-fat meal | Safety in children (including long-term safety) | Planned | Final report anticipated Q4 2013 |
| Post-authorization safety study of HIV-1 and HBV infected pediatric patients | To provide information to help establish evidence-based strategies for management of tenofovir DF-associated bone and/or renal toxicity in pediatric patients | Safety in children (including long-term safety) | Planned | Protocol synopsis to be submitted within 1 month of the CHMP Opinion on the ongoing pediatric applications. |
| ***Epidemiology Studies*** | | | | |
| GS-US-104-0353 | A Preliminary Evaluation of Fanconi Syndrome Due to Antiretroviral Therapies in HIVInfected Persons | Renal Toxicity | Ongoing | Report anticipated Q3 2012 |
| GS-US-104-0423 | A Phase 4 Cross-Sectional Study of Bone Mineral Density in HIV-1 Infected Subjects | bone mineral density | Planned | Report anticipated 21 August 2014 |
| Drug Utilization Study in HIV-1 and HBV infected pediatric patients | To provide information on the effectiveness of risk minimization measures for pediatric patients in the postmarketing setting | Safety in children (including long-term safety) | Planned | Protocol synopsis to be submitted within 1 month of the CHMP Opinion on the Ongoing pediatric applications.a Feasibility assessment results anticipated to be submitted by Q4 2012. |
| Antiretroviral Pregnancy Registry | To provide information on the risk of birth defects in patients exposed to tenofovir DF during pregnancy | Safety in pregnancy | Ongoing | Reports produced 6-monthly (June and December each year) |

| | | | | |
|---|---|---|---|---|
| Cross-sectional Study of Possible Mitochondrial Dysfunction in Children (MITOC group) | To provide information on the risk of mitochondrial disease in children exposed to NRTIs in utero) | Safety in pregnancy | Enrolment ongoing | Final report anticipated 2013/2014 |
| ***Other Data*** | | | | |
| Cumulative review of reversibility of renal tubulopathy in HIV-1 and HBV infected adult patients | To provide information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult patients) | Renal Toxicity | Planned | Review to be submitted by 31 December 2012 |
| Monitoring of reversibility of renal tubulopathy in clinical trials | To provide information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and pediatric patients | Renal Toxicity | Planned | RMP to be updated with reversibility data when available from individual CSRs |
| Retrospective analyses of pediatric BMD Z-scores adjusted by height | To provide information on BMD Z-scores adjusted by height in pediatric patients | bone mineral density | Planned | Submission of analysis results anticipated Q1 2013 |

All pharmacovigilance measures included are Category 3 - required additional PhV activity.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

***Risk minimisation measures***

**Table 32.** Summary table of Risk Minimisation Measures

| Safety Concern | Routine Risk Minimization Activities Sufficient? | If Yes, Provide Description of Routine Activity and Justification |
|---|---|---|
| **Important Identified Risks** | | |
| Renal Toxicity | No | See table below |
| Bone events due to proximal renal tubulopathy/loss of BMD | Yes | Product Labeling for Prescribers and Patients (see Sections 4.1 and 6)<br>The language that is included in the product labeling is considered sufficient to minimize the risk. |
| Post-treatment hepatic flares in HBV monoinfected and HIV-1/HBV coinfected patients | | |
| Interaction with didanosine | | |
| Pancreatitis | | |
| Lactic acidosis and severe hepatomegaly with steatosis | | |
| Lipodystrophy | | |
| **Important Potential Risks** | Yes | Product Labeling for Prescribers |

| | | |
|---|---|---|
| Development of resistance during long-term exposure in HBV infected patients | | and Patients (see Sections 4.1 and 6)<br>The language that is included in the product labeling is considered sufficient to minimize the risk. |
| **Missing Information** | Yes | Product Labeling for Prescribers and Patients (see Section 4.1) |
| Safety in children (including long-term safety) | | |
| Safety in elderly patients | | |
| Safety in pregnancy | | |
| Safety in lactation | | |
| Safety in black HBV infected patients | | |
| Safety in patients with renal impairment | | |

| **Safety Concern** | **Renal Toxicity** |
|---|---|
| Routine Risk Minimization Activities | See Section 4.1 (Product Labeling for Prescribers and Patients).<br>Updates to labeling as appropriate. |
| Additional Risk Minimization Activity | Educational initiatives |
| Objective and Rationale | Managing risk through medical education activities, primarily aimed at communicating the importance of assessing creatinine clearance ($CL_{cr}$) at baseline and during therapy, and the need for appropriate dose reduction in patients with renal impairment. |
| Proposed Actions | <u>Educational initiatives (HIV)</u> (see Section 5.2 for further details)<br>'HIV and the Kidney' educational program<br>HIV renal educational brochure (including creatinine clearance slide ruler)<br><u>Educational initiatives (HBV)</u> (see Section 5.3 for further details)<br>Renal educational program for HBV (part of 'Hepatology Perspectives' educational program)<br>HBV renal educational brochure (including creatinine clearance slide ruler)<br>The HIV and HBV renal educational brochures, which include key renal messages, are provided in Annex 7. In accordance with the CHMP's conclusions on Version 10 of the Viread EU-RMP, the creatinine clearance slide ruler has been included in updated HIV and HBV renal educational brochures. The updated brochures have been submitted to each national authority for assessment and approval prior to distribution. |
| Criteria to be Used to Verify the Success of Proposed Risk Minimization Activity | <u>HIV Survey</u><br>Gilead has conducted a HIV physician survey in Europe which was designed to formally assess the impact of key safety messages promoted by the renal educational program. Further HIV surveys were conducted in Q4 2008, Q1 2010 and Q4 2011 following the roll-out of the 'HIV and the Kidney' educational program across the EU (see Section 5.2).<br><u>HBV Survey</u><br>Gilead has conducted a HBV physician survey in Europe providing a benchmark of HBV physician knowledge and practices relating to renal management of patients with CHB. Further HBV surveys were conducted in Q2 2010 and Q4 2011 following the roll-out of the HBV renal educational program across the EU |

| Safety Concern | Renal Toxicity |
|---|---|
| | (see Section 5.3). |
| Proposed Review Period | Further waves of research will assess changes in knowledge/awareness over time following the implementation of educational campaigns. |

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

## *1.7. Update of the Product information*

**Proposed changes by MAH**

| PRESENT [10,11] | PROPOSED [10, 11] |
|---|---|
| **EN Annexes:**<br><br>ANNEX I<br><br>SUMMARY OF PRODUCT CHARACTERISTICS<br><br>4.1 Therapeutic indications<br><br>Hepatitis B infection<br><br>Viread is indicated for the treatment of chronic hepatitis B (see section 5.1) in adults with:<br><br>• compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.<br><br>• decompensated liver disease (see sections 4.4, 4.8 and 5.1). | **EN Annexes:**<br><br>ANNEX I<br><br>SUMMARY OF PRODUCT CHARACTERISTICS<br><br>4.1 Therapeutic indications<br><br>Hepatitis B infection<br><br>Viread is indicated for the treatment of chronic hepatitis B ~~(see section 5.1)~~ in adults with:<br><br>• compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis **(see section 5.1)**.<br><br>• **compensated liver disease and genotypic evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).**<br><br>• decompensated liver disease (see sections 4.4, 4.8 and 5.1). |
| 4.8 Undesirable effects<br><br>Hepatitis B clinical studies: | 4.8 Undesirable effects<br><br>Hepatitis B clinical studies:<br><br>**Patients with lamivudine-resistant chronic hepatitis B: No new adverse reactions to tenofovir disoproxil fumarate were identified from a randomised, double-blind study (GS-US-174-0121) in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil fumarate (n = 141) or emtricitabine/tenofovir disoproxil fumarate (n = 139) for 96 weeks.** |

| PRESENT [10,11] | PROPOSED [10, 11] |
|---|---|
| 5.1 Pharmacodynamic properties<br><br>Data pertaining to HBV: | 5.1 Pharmacodynamic properties<br><br>Data pertaining to HBV:<br><br>***Experience in patients with lamivudine-resistant chronic hepatitis B at 96 weeks:*** **The efficacy and safety of 245 mg tenofovir disoproxil (as fumarate) or a fixed dose combination of 200 mg emtricitabine plus 245 mg tenofovir disoproxil (as fumarate) were evaluated in a randomised, doubleblind study (Study GS-US-174-0121), in HBeAg-positive and HBeAg-negative patients with viraemia (HBV DNA ≥ 1000 IU/ml) and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). One hundred forty-one and 139 adult subjects were randomised to the tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate treatment arms, respectively. Subjects randomised to tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate treatment arms had a mean age of 47 years (range 18-73) and 46 years (range 18 to 72), 74% and 77% were male, 59% and 64% were Caucasian, and 37% and 30% were Asian, respectively. At baseline in the tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate treatment arms, 54% and 51% of subjects were HBeAg-negative, 46% and 49% were HBeAg-positive, mean HBV DNA levels were 6.4 and 6.5 log10 copies/ml, and mean ALT was 71 U/L and 87 U/L, respectively. After 96 weeks of treatment, 126 of 141 subjects (89%) randomised to tenofovir disoproxil fumarate had HBV DNA < 400 copies/ml, and 49 of 79 subjects (62%) had ALT normalisation. After 96 weeks of treatment with emtricitabine plus tenofovir disoproxil fumarate, 120 of 139 subjects (86%) had HBV DNA < 400 copies/ml, and 52 of 83 subjects (63%) had ALT normalisation. Among the HBeAg-positive subjects randomised to tenofovir disoproxil fumarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96.** |

| PRESENT [10,11] | PROPOSED [10, 11] |
|---|---|
| 5.1 Pharmacodynamic properties (continued)<br><br>Data pertaining to HBV: | 5.1 Pharmacodynamic properties (continued)<br><br>Data pertaining to HBV:<br><br>**In the HBeAg-positive subjects randomised to emtricitabine plus tenofovir disoproxil fumarate, 9 of 68 subjects (13%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti-HBe seroconversion through Week 96. No subject randomised to tenofovir disoproxil fumarate experienced HBsAg loss or seroconversion to anti-HBs. One subject randomised to emtricitabine plus tenofovir disoproxil fumarate experienced HBsAg loss.** |
| 5.1 Pharmacodynamic properties<br><br>Data pertaining to HBV:<br><br>Clinical resistance: | 5.1 Pharmacodynamic properties<br><br>Data pertaining to HBV:<br><br>Clinical resistance:<br><br>**In Study GS-US-174-0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil fumarate for up to 96 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6 of 9 patients with HBV DNA > 400 copies/ml at their last time point on tenofovir disoproxil fumarate. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.** |

10 Specify the precise present and proposed wording or specification, including dossier section number(s) at the lowest possible level.
11 For SPC, labelling and package leaflet changes, underline or highlight the changed words presented in the table above or provide as a separate Annex

1. The MAH proposed to update SmPC section 4.1 to add the indication for treatment of chronic hepatitis B in adults with compensated liver disease and genotype evidence of lamivudine resistant hepatitis B virus.

A change to the proposal has been made in the light of the CHMP's recommendation not to restrict the indication to compensated liver disease only, in such patients (highlighted).

**Section 4.1 "Therapeutic indication"**

*Hepatitis B infection*

Viread 245 mg film-coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).
- ~~compensated liver disease and evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).~~
- **evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1)."**

- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

2. The MAH proposed to update SmPC section 4.8 to reflect safety consequences obtained from study GS-US-174-0121.

**Section 4.8 "Undesirable effects"**

*Patients with lamivudine-resistant chronic hepatitis B:* No new adverse reactions to tenofovir disoproxil fumarate were identified from a randomised, double-blind study (GS-US-174-0121) in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil fumarate (n = 141) or emtricitabine/tenofovir disoproxil fumarate (n = 139) for 96 weeks.

3. The MAH proposed to update SmPC section 5.1 to include the study GS-US-174-0121 description and results including information on genotypic data.

The CHMP considered that the description of the study results in section 5.1 could be shortened.

Additional changes have been made in the light of the MAH's response to the RSI (highlighted).

**Section 5.1 "Pharmacological properties"**

*Experience in patients with lamivudine-resistant chronic hepatitis B at 96 weeks:* The efficacy and safety of 245 mg tenofovir disoproxil (as fumarate) was evaluated in a randomised, double-blind study (GS-US-174-0121) in HBeAg positive and HBeAg negative patients **(n=280) with compensated liver disease**, with viraemia (HBV DNA ≥ 1000 IU/ml) and genotypic evidence of lamivudine resistance (rtM204I/V +/-rtL180M). **Only five had ADV-associated resistance mutations at baseline.** One hundred forty-one and 139 adult subjects were randomised to a tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate treatment arm, respectively. Baseline demographics were similar between the two treatment arms: At baseline, 52.5% of subjects were HBeAg negative, 47.5% were HBeAg positive, mean HBV DNA level was 6.5 log10 copies/ml, and mean ALT was 79 U/l, respectively.

After 96 weeks of treatment, 126 of 141 subjects (89%) randomised to tenofovir disoproxil fumarate had HBV DNA < 400 copies/ml, and 49 of 79 subjects (62%) had ALT normalisation. After 96 weeks of treatment with emtricitabine plus tenofovir disoproxil fumarate, 120 of 139 subjects (86%) had HBV DNA < 400 copies/ml, and 52 of 83 subjects (63%) had ALT normalisation. Among the HBeAg positive subjects randomised to tenofovir disoproxil fumarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through week 96. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil fumarate, 9 of 68 subjects (13%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti-HBe seroconversion through week 96. No subject randomised to tenofovir disoproxil fumarate experienced HBsAg loss or seroconversion to anti-HBs. One subject randomised to emtricitabine plus tenofovir disoproxil fumarate experienced HBsAg loss. ~~The efficacy of tenofovir disoproxil fumarate in patients with high baseline viral load (>107 copies/ml), prior adefovir dipivoxil experience, or prior entecavir experience or entecavir resistance was similar to those without these factors.~~

*Clinical resistance*

[…]

In study GS-US-174-0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil fumarate for up to 96 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6 of 9 patients with HBV DNA > 400 copies/ml at their last

time point on tenofovir disoproxil fumarate. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

As a consequence of this variation, sections 4.1, 4.8 and 5.1 of the SmPC have been updated.

Furthermore, the MAH took the opportunity of this variation to perform minor linguistic amendments for the CZ and DE annexes. Also, a factual error in the Estonian SmPC section 5.1 is corrected.

Annex II and Labelling are updated in accordance to latest guidance.

# 2. Benefit-Risk Balance

## Benefits

## Beneficial effects

At week 96, a similarly high proportion of patients achieved viral suppression in both treatment groups (TDF: 89.4% vs TDF/FTC: 86.3%). Viral potency is also observed with the most stringent criterion of HBV DNA <169 copies/ml and comparable results were observed between both treatments arms at week 96 on all (virological, biochemical and serological) endpoints. Those results are in line with those reported in patients without lamivudine resistance and confirm that TDF is highly effective in patients with LAM-R (at least in those harbouring rtM204V/I +/-rtL180M).

## Uncertainty in the knowledge about the beneficial effects

Although high viral response rate is achieved, it remains that the level of translation into HBe (and HBs) seroconversion remains limited. However, it is acknowledged that literature reports lower rates of seroconversion in patients with LAM R as compared to patients with wild type.

Moreover, whether TDF+FTC would not be more beneficial than TDF monotherapy in patients having pejorative criteria (such as high viral load, prior ADV experience, with or without rtA181T resistance mutation, prior ETV exposure) cannot be ascertained from the study submitted given the limited number of patients cumulating pejorative criteria.

## Risks

## Unfavourable effects

This study did not add any new safety issue to the already known risks for renal and bone toxicity of TDF.

## Uncertainty in the knowledge about the unfavourable effects

The long term impact of renal and bone toxicity is a concern that is to be kept under close scrutiny.

The MAH conducted an ad hoc analyses of key safety results (AEs, renal-laboratory assessments, and BMD) in renal impaired subjects (n= 74 patients with mild renal impairment) compared with subjects with normal renal function (n=206). Although there was no apparent signal towards a significant alteration of renal safety in patients with mild renal impairment, this cannot be regarded as sufficient to derive full reassurance in these patients. This will have to be kept under scrutiny through the RMP and PSUR.

An unexpected pattern of decrease in hip BMD was observed, with gradual decrease not reaching a plateau at Week 96. Even though mean change from baseline in hip BMD remains small, this will need to be closely monitored in longer term reports and the potential for bone toxicity should continue to be monitored in future PSURs.

### Benefit-Risk Balance

### Discussion on the Benefit-Risk Balance

As previously observed in naïve patients, TDF also demonstrated high virologic potency and genetic barrier in lamivudine-resistant patients. As for naïve patients, the benefit-risk balance of tenofovir for the treatment of adults with lamivudine resistant chronic hepatitis B is positive.

Even though patients with decompensated CHB were not specifically enrolled in this study in LAM-R, it is considered that due to its high potency and genetic barrier, the lack of cross-resistance between TDF and LAM, and in view of the clinical experience already gained in decompensated patients (study GS-US-174-0108), tenofovir is also a valid option in patients with LAM-R and decompensated CHB.

# 3. Recommendations

The application for the extension of the indication for the treatment of adults with lamivudine resistant chronic hepatitis B is approvable since other concerns have all been resolved.

### *Final Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a – Change to therapeutic indication - Addition of a new therapeutic indication or modification of an approved one | II |

Extension of the indication: Treatment of adults with lamivudine resistant chronic hepatitis B. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC were updated.

Annex I and IIIa were updated to reflect the fact that the EDQM short standard term ‘tablet(s)’ was introduced into the Viread packaging.

Furthermore, the PI was brought in line with the latest QRD template version 8 An update was agreed to include minor linguistic amendments for the CZ and DE annexes. A factual error in the Estonian SmPC was corrected.

Amendments to the SmPC, Annex II and Labelling were approved.

### *Conditions and requirements of the marketing authorisation*

#### *Risk management system and PSUR cycle*

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

## • Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

## • Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Viread in adults and/or paediatric patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

The HIV and HBV renal educational brochures should contain the following key messages:

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks
- The importance of dose interval adjustment of Viread in adult patients with creatinine clearance of 30-49 ml/min
- That Viread is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). If no alternative treatment is available, prolonged dose intervals may be used
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Viread therapy

- Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric educational brochures should contain the following key messages:

- That a multidisciplinary approach is recommended for the management of paediatric patients
- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread is not recommended for use in paediatric patients with renal impairment
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Viread treatment
- That Viread may cause a reduction in BMD and the effects of Viread associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained